PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re:	U.S. Patent 5,691,336
Issued:	November 25, 1997
Application No:	08/525,870
To:	Conrad P. Dorn, et al.
Assignee:	Merck & Co., Inc.
For:	MORPHOLINE COMPOUNDS ARE PRODRUGS USEFUL AS TACHYKININ RECEPTOR ANTAGONISTS

Mail Stop Patent Extension
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPLICATION FOR EXTENSION OF PATENT TERM
UNDER 35 U.S.C. § 156

Sir:

Applicant, Merck & Co., Inc. a corporation organized and existing under the laws of the State of New Jersey, and having a place of business at 126 East Lincoln Ave., Rahway, NJ 07065-0907, United States of America, represents that it is the assignee of the entire interest in and to Letters Patent of the United States No. 5,691,336 granted to Conrad P. Dorn, et al. on November 25, 1997, for "Morpholine Compounds Are Prodrugs Useful As Tachykinin Receptor Antagonists" by virtue of an assignment in favor of Merck & Co., Inc., recorded in the United States Patent and Trademark Office (hereinafter referred to as "the Patent Office") on August 11, 1997, at Reel 8654, Frame 0863. A copy of the Assignment and the Notice of Recordation is enclosed as "**Exhibit A**". A Power of Attorney is attached as "**Exhibit B**" confirming that the undersigned registered practitioner is authorized to act on behalf of the Applicant.

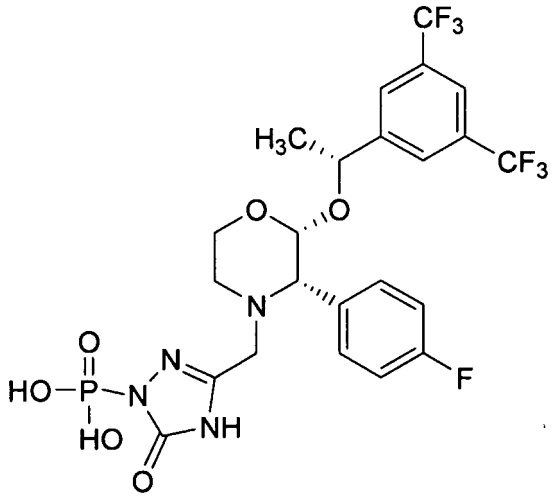
Pursuant to the provisions of 37 C.F.R. § 1.730, Applicant hereby requests an extension of patent term under 35 U.S.C. § 156, by providing the following materials set forth herein and in the accompanying papers. For the convenience of the Patent Office, the information contained in this application is presented in a format that follows the order of the requirements of 37 C.F.R. § 1.740(a).

(1) Identification of the Approved Product [§1.740(a)(1)]

The approved product is EMEND for Injection (fosaprepitant dimeglumine). The active ingredient of the approved product, EMEND for Injection, is fosaprepitant dimeglumine, a pharmaceutically acceptable salt of fosaprepitant. Fosaprepitant is a phosphoramidate prodrug of aprepitant, which is the active ingredient in the previously approved product EMEND. Fosaprepitant and fosaprepitant dimeglumine are further identified as follows:

USAN Name: Fosaprepitant

Chemical Structural Formula:



Chemical Name:
[3-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-2,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]phosphonic acid

Alternate Chemical Name:

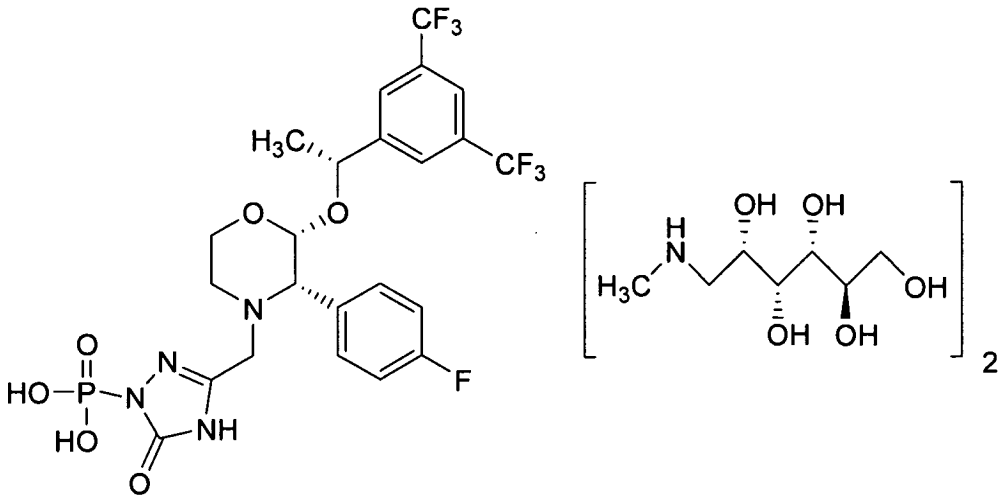
2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1-phosphoryl-5-oxo-4H-1,2,4-triazolo)methylmorpholine

Molecular Formula:

$C_{23}H_{22}F_7N_4O_6P$

USAN Name: Fosaprepitant dimeglumine

Chemical Structural Formula:



Chemical Name:

1-deoxy-1-(methylamino)-D-glucitol[3-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]-ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-2,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]phosphonate (2:1) (salt)

Alternate Chemical Name:

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1-phosphoryl-5-oxo-4H-1,2,4-triazolo)methylmorpholine, bis(N-methyl-D-glucamine)

Molecular Formula:

$C_{23}H_{22}F_7N_4O_6P \cdot 2(C_7H_{17}NO_5)$

(2) Federal Statute Governing Regulatory Approval of the Approved Product [§1.740(a)(2)]

EMEND for Injection was subject to regulatory review under Section 505(b) of the Federal Food, Drug and Cosmetic Act, Section 505 (21 U.S.C. § 355).

(3) Date of Approval for Commercial Marketing [§1.740(a)(3)]

EMEND for Injection received permission for commercial marketing or use under Section 505(b) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355) on January 25, 2008. EMEND for Injection was approved for use, in combination with other antiemetic agents, for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin, and the prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy. A copy of the letter from the FDA approving marketing of EMEND for Injection is attached as "**Exhibit C**". A copy of the approved label for EMEND for Injection is attached as "**Exhibit D**".

(4) Identification of Active Ingredient and Certifications Related to Commercial Marketing of Approved Product [§1.740(a)(4)]

The active ingredient of EMEND for injection is fosaprepitant dimeglumine, a pharmaceutically acceptable salt of fosaprepitant. Neither fosaprepitant dimeglumine nor any salt or ester of fosaprepitant dimeglumine has previously been approved in an application filed under section 505 of the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act prior to the approval of NDA 22-023 by the Federal Food and Drug Administration on January 25, 2008. In addition, neither fosaprepitant nor any salt or ester of fosaprepitant has previously been approved in an application filed under section 505 of the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act prior to the approval of NDA 22-023 by the Federal Food and Drug Administration on January 25, 2008.

(5) Statement Regarding Timeliness of Submission of Patent Term Extension Request [§1.740(a)(5)]

This application for extension of patent term under 35 U.S.C. § 156 is being submitted within the sixty (60) day period permitted for submission pursuant to 37 C.F.R. § 1.720(f). The date of the last day on which the application could be submitted is March 25, 2008. The present application, therefore, is timely submitted.

(6) Complete Identification of the Patent for Which Extension Is Being Sought [§1.740(a)(6)]

The patent for which extension is being sought is identified as follows:

Inventors: Conrad P. Dorn
Jeffrey J. Hale
Malcolm MacCoss
Sander G. Mills

Patent No.: 5,691,336

Title: Morpholine Compounds Are Prodrugs Useful As Tachykinin Receptor Antagonists

Date of Issue: November 25, 1997

Expires: March 4, 2014

(7) Copy of the Patent for Which an Extension is Being Sought [§1.740(a)(7)]

A copy of Patent No. 5,691,336, the patent for which an extension is being sought, is attached hereto as "**Exhibit E**".

(8) Copies of Disclaimers, Certificates of Correction, Receipt of Maintenance Fee Payment, or Reexamination Certificate [§1.740(a)(8)]

Copies of the maintenance fee statements for US Patent No. 5,691,336 are attached as "**Exhibit F**" and indicate that the maintenance fees have been duly paid. A certificate of correction for US Patent No. 5,691,336 has been filed on March 20, 2008 (copy attached at "**Exhibit E**"). No disclaimer or reexamination certificate has been filed and/or issued for US Patent No. 5,691,336.

(9) Statement Regarding Patent Claims Relative to Approved Product [§1.740(a)(9)]

The statements provided herein are made solely to comply with the requirements of 37 C.F.R §1.740(a)(9). Applicant notes that, as the M.P.E.P. acknowledges, the requirement of 37 C.F.R. §1.740(a)(9) does not require an applicant to show whether or how the listed claims would be infringed, and that this question cannot be answered without specific knowledge concerning acts performed by third parties. As such, these comments are not an assertion or an admission of Applicant as to the scope of the listed claims, or whether or how any of the listed claims would be infringed, literally or under the doctrine of equivalents, by the manufacture, use, sale, offer for sale or the importation of any product.

U.S. Patent No. 5,691,336 claims the approved product and pharmaceutical compositions comprising the approved product. In U.S. Patent No. 5,691,336, Claims 1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, and 19 claim the approved product *per se*, and Claims 20 and 23 claim a pharmaceutical composition which comprises the approved product.

Pursuant to M.P.E.P. §2573 and 37 C.F.R. §1.740(a)(9), the following explanation is provided to demonstrate the manner in which at least one such patent claim reads on the approved product or a method of making or using the approved product.

Claim 14 of U.S. Patent No. 5,691,336 reads:

14. A compound which is:

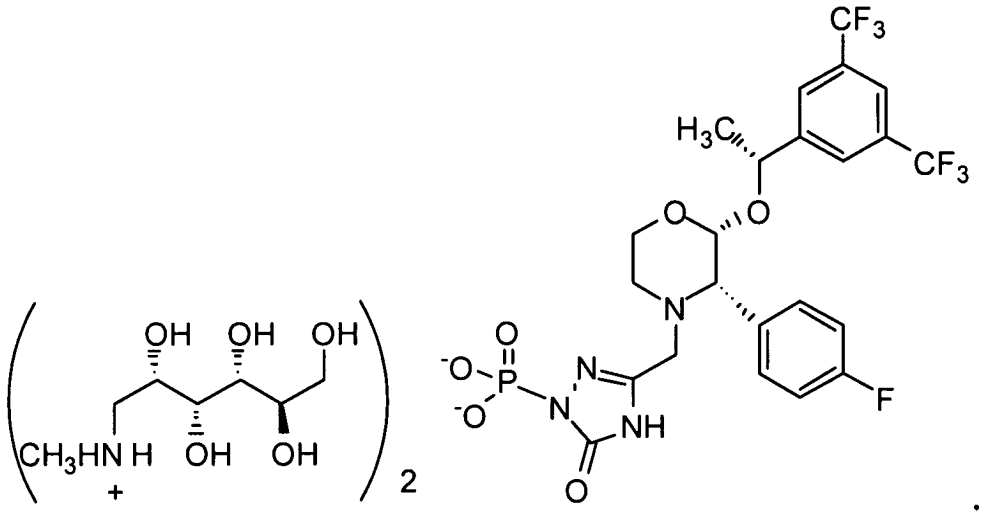
2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)
-(4-fluoro)phenyl-4-(3-(1-phosphoryl-5-oxo-4H-1,2,4-
triazolo)methylmorpholine;

or a pharmaceutically acceptable salt thereof.

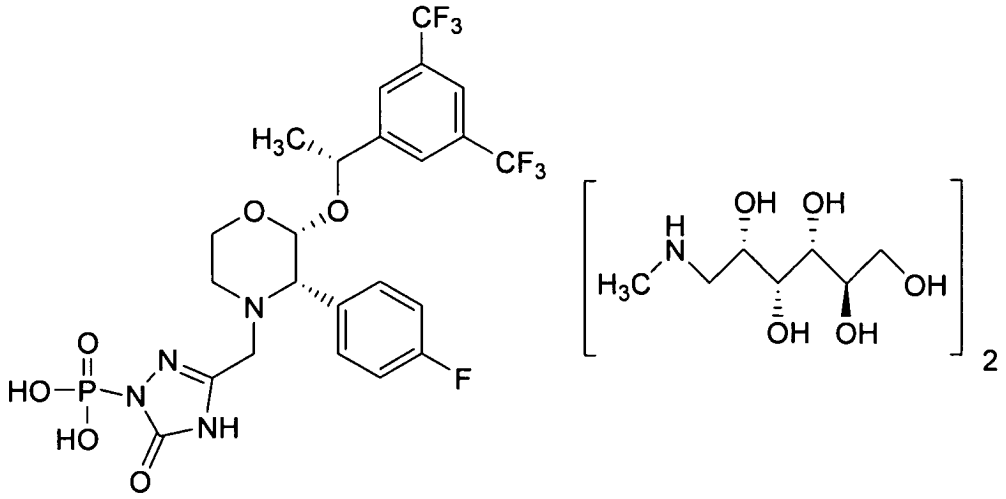
Claim 14 of U.S. Patent No. 5,691,336 claims fosaprepitant (i.e. 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1-phosphoryl-5-oxo-4H-1,2,4-triazolo)methylmorpholine) or any pharmaceutically acceptable salt thereof, including fosaprepitant dimeglumine, which is the active ingredient in the approved product EMEND for Injection

Claim 19 of U.S. Patent No. 5,691,336 reads:

19. A compound which is:



Claim 19 of U.S. Patent No. 5,691,336 specifically claims fosaprepitant dimeglumine, which is the active ingredient in the approved product EMEND for Injection:



10. Relevant Dates Under 35 U.S.C. § 156 for Determination of Applicable Regulatory Review Period [§1.740(a)(10)]

The relevant dates and information pursuant to 35 U.S.C. § 156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(a) IND Effective Date [35 U.S.C. §156(a)(1)(B)(i); 37 C.F.R §1.740(a)(10)(i)(A)]

Investigational New Drug Application (IND 48,924) for fosaprepitant was submitted on September 28, 1995, and the IND became effective on October 28, 1995.

(c) NDA Submission Date [35 U.S.C. §156(g)(1)(B)(i); 37 C.F.R. § 1.740(a)(10)(i)(B)]

New Drug Application (NDA 22-023) for fosaprepitant was submitted on March 31, 2006.

(d) NDA Issue Date [35 U.S.C. §156(g)(1)(B)(ii); 37 C.F.R. §I.740(a)(10)(i)(C)]

New Drug Application (NDA 22-023) for fosaprepitant was approved on January 25, 2008.

(11) Summary of Significant Events During Regulatory Review Period [§1.740(a)(11)]

As a brief description of the significant activities undertaken by Applicant, Merck & Co., Inc., during the applicable regulatory review period, attached hereto as "**Exhibit G**", is a chronology of the major communications between the Applicant and the FDA from September 28, 1995 to January 25, 2008.

In this regard, Applicant notes that approval of New Drug Application (NDA 22-023) for fosaprepitant was based, in part, by reference to some of the clinical studies that were conducted with aprepitant (under NDA 21-549). Fosaprepitant, a prodrug of aprepitant, when administered intravenously to a patient is rapidly converted to aprepitant.

In "**Exhibit G**", the "Compound ID" = 0517 corresponds to fosaprepitant (i.e. Merck Development Number MK-0517), and the "Compound ID" = 0869 corresponds to aprepitant (i.e. Merck Development Number MK-0869). The "Reg Number" = 48,924 corresponds to the IND for fosaprepitant (Compound ID 0517), and the "Reg Number" = 50,283 corresponds to the IND for aprepitant (Compound ID 0869). The "Reg Number" = 22-023 corresponds to the NDA for fosaprepitant (Compound ID 0517), and the "Reg Number" = 21-549 corresponds to the NDA for aprepitant (Compound ID 0869).

(12) Statement Concerning Eligibility for and Duration of Extension Sought Under §156 [§ 1.740(a)(12)]

(12)(A) Applicant is of the opinion that U.S. Patent 5,691,336 is eligible for extension under 35 U.S.C. § 156 because it satisfies all of the requirements for such extension as follows:

(a) 35 U.S.C. § 156(a)
U.S. Patent 5,691,336 claims the approved product.

(b) 35 U.S.C. § 156(a)(1)
The term of U.S. Patent 5,691,336 has not expired before submission of this application under 35 U.S.C. § 156(d)(1) for its extension.

(c) 35 U.S.C. § 156(a)(2)
The term of U.S. Patent 5,691,336 has never been extended under 35 U.S.C. § 156(e)(1).

(d) 35 U.S.C. § 156(a)(3)
The application for extension is submitted by the owner of record and is in accordance with the requirement of 35 U.S.C. § 156(d) and rules of the U.S. Patent and Trademark Office.

(e) 35 U.S.C. § 156(a)(4)
The product, EMEND for Injection, has been subject to a regulatory review period before its commercial marketing or use.

(f) 35 U.S.C. § 156(a)(5)(A)
The permission for the commercial marketing or use of the product, EMEND for Injection, after the regulatory review period is the first permitted commercial marketing or use of the product under the provision of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355) under which such regulatory review period occurred.

(g) 35 U.S.C. § 156(c)(4)
No other patent has been extended for the same regulatory review period for the product, EMEND for Injection.

(12)(B) The length of extension of the patent term of U.S. Patent 5,691,336 claimed by Applicant is 1826 days (or 5 years). The length of the extension was determined pursuant to 37 C.F.R. § 1.775 as follows:

(a) The regulatory review period under 35 U.S.C. 156(g)(1)(B) began on October 28, 1995, and ended on January 25, 2008, which is a total of 4473 days which is the sum of (i) and (ii) below:

(i) The period of review under 35 U.S.C. 156(g)(2)(B)(i), the "Testing Period," began on October 28, 1995 and ended on March 31, 2006, which is 3808 days; and

(ii) The period of review under 35 U.S.C. 156(g)(2)(B)(ii), the "Application Period," began on March 31, 2006, and ended on January 25, 2008, which is 665 days;

(b) The regulatory review period upon which the period of extension is calculated is the entire regulatory review period as determined in sub-paragraph (12)(B)(a) above (4473 days) less

(i) The number of days in the regulatory review period which were on or before the date on which the patent issued (October 28, 1995 to November 25, 1997) which is 760 days, and

(ii) The number of days during which applicant did not act with due diligence which is zero (0) days, and

(iii) One-half the number of days determined in sub-paragraph (12)(B)(a)(i) after the patent issued [(3808 – 760)/2] or 1524 days;

(iv) The regulatory period is calculated by subtracting the number of days determined in sub-paragraph (12)(B)(b)(i)-(iii) from the entire regulatory review period as determined in sub-paragraph (12)(B)(a) (which is 4473 days – 760 days – 0 days – 1524 days) which equals 2189 days;

(c) The number of days as determined in sub-paragraph (12)(B)(b)(iv) (2189 days) when added to the original term of the patent (March 4, 2014, as determined by 35 U.S.C. § 154 (c) and 37 C.F.R. § 1.321) would result in the date, March 1, 2020;

(d) Fourteen (14) years when added to the date of NDA approval (January 25, 2008) would result in the date January 25, 2022;

(e) The earlier date as determined in sub-paragraphs (12)(B)(c) and (12)(B)(d) is March 1, 2020;

(f) Since the original patent was issued after September 24, 1984, the extension obtainable is limited to not more than five years. Five years when added to the original expiration date of the patent (March 4, 2014) would result in the date, March 4, 2019;

(g) The earlier date as determined in sub-paragraph (12)(B)(e) and (12)(B)(f) is March 4, 2019, which is 1826 days (or 5 years) extension from the expiration date of the patent.

(13) Statement Pursuant to 37 C.F.R. [§1.740(a)(13)]

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought, particularly as that duty is defined in 37 C.F.R. §1.765.

(14) Applicable Fee [§1.740(a)(14)]

The prescribed fee of $1,120.00 in accordance with 37 C.F.R. § 1.20(j)(1) for receiving and acting upon this application for extension is to be charged to Merck Deposit Account No. 13-2755 as authorized in the attached Fee Sheet, which is submitted in duplicate.

(15) Name and Address for Correspondence [§1.740(a)(15)]

Please address all inquiries and correspondence relating to the application for patent term extension to:

J. Eric Thies
Merck & Co., Inc.
Patent Department
P.O. Box 2000
Rahway, New Jersey 07065-0907
Telephone: (732) 594-3904
Facsimile: (732) 594-4720

(16) Additional Copies of the Application for Extension [§1.740(b)]

Pursuant to 37 C.F.R. § 1.740(b), the instant application for extension of the patent term of U.S. Patent No. 5,691,336 is being submitted as one original and TWO additional copies thereof. Pursuant to M.P.E.P § 2753 an additional TWO copies are also enclosed herewith. Applicant hereby certifies that the copies submitted herein are true copies of the original.

Transmitted herewith in ONE ORIGINAL and FOUR COPIES total is the application for extension of the patent term of U.S. Patent No. 5,691,336 under 35 U.S.C. §156. Please charge the prescribed fee of $1,120.00 in accordance with 37 C.F.R. § 1.20(j)(1) for receiving and acting upon this application for extension to Merck Deposit Account No. 13-2755.

Respectfully submitted,

By _____

J. Eric Thies
Reg. No. 35,382
Attorney for Applicant

MERCK & CO., INC.
P.O. Box 2000
Rahway, New Jersey 07065-0907
(732) 594-3904

Date: March 20, 2008

Attachments:

- **Fee Sheet**
- "**Exhibit A**" - Assignment and Notice of Recordation
- "**Exhibit B**" - Power of Attorney
- "**Exhibit C**" - Letter from the FDA approving marketing of EMEND for Injection
- "**Exhibit D**" - Approved label for EMEND for Injection
- "**Exhibit E**" - U.S. Patent No. 5,691,336
- "**Exhibit F**" - Maintenance Fee Statements for U.S. Patent No. 5,691,336
- "**Exhibit G**" - Chronology of Major Communications with the FDA

CERTIFICATION

The undersigned hereby certifies that this application for extension of patent term under 35 U.S.C. § 156 including its attachments and supporting papers is being submitted as one original and four copies thereof.

By 

J. Eric Thies
Reg. No. 35,382
Attorney for Applicant

MERCK & CO., INC.
P.O. Box 2000
Rahway, New Jersey 07065-0907
(732) 594-3904

Date: March 20, 2008

MISC. FEE TRANSMITTAL

Patent fees are subject to annual revision.

TOTAL AMOUNT OF PAYMENT	$1,120

Complete if Known	
Application Number	08/525,870
Filing Date	September 8, 1995
First Named Inventor	Conrad P. Dorn
Examiner Name	F. Higel
Group Art Unit	1201
Attorney Docket Number	19189IA

METHOD OF PAYMENT

☒ Deposit Account

Deposit Account Number: 13-2755 Deposit Account Name: Merck & Co., Inc.

The Director is authorized to:

☒ Charge fee(s) indicated below ☒ Credit any overpayments

☒ Charge any additional fee(s) or underpayments of fee(s) under 37 CFR 1.16 and 1.17

FEE CALCULATION

FEES
Large Entity

Fee Code	Fee ($)	Fee Description	Fee Paid
1051	130	Surcharge - late filing fee or oath	
1053	130	Non-English Specification	
1812	2,520	For filing a request for *ex parte* reexamination	
1402	510	Filing a brief in support of an appeal	
1452	510	Petition to revive - unavoidable	
1453	1,540	Petition to revive - unintentional	
1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	Submission of Information Disclosure Statement	
1809	810	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	810	For each additional invention to be examined (37 CFR 1.129(b))	
1840	130	Statutory Terminal Disclaimer under 37 CFR 1.321	
		Other fee (specify) Extension of Term of Patent 37 CFR 1.20(j)(1) (Fee Code 1457)	1,120
		Other fee (specify)	

TOTAL $1,120

SUBMITTED BY				Complete (if applicable)	
Typed or Printed Name	J. Eric Thies			Reg. Number	35,382
Signature	J. Eric Thies	Date	03/20/2008	Deposit Account User ID	

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		Other fee (specify)	

TOTAL $1,120

SUBMITTED BY				Complete (if applicable)	
Typed or Printed Name	J. Eric Thies			Reg. Number	35,382
Signature	J. Eric Thies	Date	03/20/2008	Deposit Account User ID	

MISC. FEE TRANSMITTAL

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Filing Date	September 8, 1995
First Named Inventor	Conrad P. Dorn
Examiner Name	F. Higel
Group Art Unit	1201
Attorney Docket Number	19189IA

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Deposit Account Number: 13-2755 Deposit Account Name: Merck & Co., Inc.

The Director is authorized to:

☒ Charge fee(s) indicated below ☒ Credit any overpayments

☒ Charge any additional fee(s) or underpayments of fee(s) under 37 CFR 1.16 and 1.17

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MAR 21 2008
PATENT EXTENSION
OPLA

FEE CALCULATION

FEES
Large Entity

Fee Code	Fee ($)	Fee Description	Fee Paid
1051	130	Surcharge - late filing fee or oath	
1053	130	Non-English Specification	
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1840	130	Statutory Terminal Disclaimer under 37 CFR 1.321	
		Other fee (specify) Extension of Term of Patent 37 CFR 1.20(j)(1) (Fee Code 1457)	1,120
		Other fee (specify)	

TOTAL $1,120

SUBMITTED BY				Complete (if applicable)	
Typed or Printed Name	J. Eric Thies			Reg. Number	35,382
Signature	J. Eric Thies	Date	03/20/2008	Deposit Account User ID	

EXHIBIT A

Assignment and Notice of Recordation

19189IA

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SEPTEMBER 11, 1997

PTAS

MERCK & CO., INC.
J. ERIC THIES
PATENT DEPARTMENT
P.O. BOX 2000 --RY60-30
RAHWAY, N.J. 07065-0907

100520216A

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, NORTH TOWER BUILDING, SUITE 10C35, WASHINGTON, D.C. 20231.

RECORDATION DATE: 08/11/1997

REEL/FRAME: 8654/0863
NUMBER OF PAGES: 3

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
DORN, CONRAD P. — DOC DATE: 09/08/1995

ASSIGNOR:
HALE, JEFFREY J. — DOC DATE: 09/08/1995

ASSIGNOR:
MACCOSS, MALCOLM — DOC DATE: 09/08/1995

ASSIGNOR:
MILLS, SANDER G. — DOC DATE: 09/08/1995

ASSIGNEE:
MERCK & CO., INC.
P.O. BOX 2000, RY60-30
RAHWAY, NEW JERSEY 07065-0907

SERIAL NUMBER: 08525870 — FILING DATE: 09/08/1995
PATENT NUMBER: — ISSUE DATE:

TARA WASHINGTON, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on the date appearing below.

MERCK & CO., INC. 7 August 1997

By J. Eric Thies Date

08-29-1997

100520216

Patent Case No. 19189IA

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

RECORDATION FORM COVER SHEET
PATENTS ONLY

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TO THE HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS: PLEASE RECORD THE ATTACHED ORIGINAL DOCUMENTS OR COPY THEREOF.

1. Name(s) of Conveying party(ies):
CONRAD P. DORN, JEFFREY J. HALE, MALCOLM MACCOSS AND SANDER G. MILLS

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

2. Nature of conveyance:
- ☒ Assignment
- ☐ Merger
- ☐ Security Agreement
- ☐ Change of Name
- ☐ Other:

Execution Date: Sep 8, 1995

3. Name and address of receiving party(ies):
Name: MERCK & CO., INC.
Internal Address: RY60-30
Street Address: P.O. Box 2000
City & State: RAHWAY, NEW JERSEY
Zip: 07065-0907

Additional name(s) & addresses attached? ☐ Yes ☒ No

4. Application number(s) or patent number(s) are as follows:
(a) Patent Application No(s). 08/525,870 , filed on Sep 8, 1995 , and titled:
MORPHOLINE COMPOUNDS ARE PRODRUGS USEFUL AS TACHYKININ RECEPTOR ANTAGONISTS

(b) If this document is being filed together with a new application, the execution date of the application:

Additional numbers attached? ☐ Yes ☒ No

5. Name & address of party to whom correspondence concerning documents should be mailed:
Name: J. ERIC THIES
Internal Address: PATENT DEPARTMENT
MERCK & CO., INC.
P.O. BOX 2000 -- RY60-30
City & State: RAHWAY, N.J. Zip: 07065-0907

6. Total no. of applications & patents involved:

7. Total fee (37 CFR 3.41).....$ 40.00
☐ Enclosed
☒ The Commissioner is hereby authorized to charge deposit account number 13-2755 for any fees which may be required or to credit any overpayment.

DO NOT USE THIS SPACE

08/07/1997 VBROWN 00000248 DA#:132755 08525870
01 FC:201 40.00 CH

8. Statement and signature:
To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

J. ERIC THIES	Reg. No. 35,382	J. Eric Thies	8/7/97
Name of Person Signing		Signature	Date

Total number of pages including cover sheet, attachments, and document: 3

Do Not Detach This Portion

Mail documents to be recorded with the required cover sheet information to: Commissioner of Patents and Trademarks
Box Assignments
Washington, D.C. 20231

Rev. 8/5/93

R/F # 8654/0869
Rec 8/11/97

PATENT
JOINT Merck Case 19189IA
U.S. Serial No. 08/525,870
Filing Date 9/8/95

ASSIGNMENT AND AGREEMENT

For value received, we, CONRAD P. DORN, JEFFREY J. HALE, MALCOLM MACCOSS, AND SANDER G. MILLS

of 972 FERNWOOD AVE, PLAINFIELD, NJ 07062; 233 HAZEL AVENUE, WESTFIELD, NJ 07090; 48 ROSE COURT, FREEHOLD, NJ 07728; AND 13A WOODBRIDGE TERRACE, WOODBRIDGE, NJ 07095; RESPECTIVELY

hereby sell, assign and transfer to MERCK & CO., Inc., a corporation of the State of New Jersey, having an office at Lincoln Avenue, City of Rahway, State of New Jersey, and it successors, assigns and legal representatives, the entire right, title and interest, for all countries, in and to certain inventions relating to

MORPHOLINE COMPOUNDS ARE USEFUL AS TACHYKININ RECEPTOR ANTAGONISTS

described in an application for Letters Patent of the United States, executed by each of us on even date herewith, or executed on the date shown in the Declaration and Power of Attorney relating to said application, and all the rights and privileges, including any and all benefits under the International Convention for the Protection of Industrial Property and related treaties, under any and all Letters Patents which may be granted in any foreign country, and under any and all extensions, divisionals, reissues and continuations of said Letters Patents.

We request that any and all Patents for said inventions be issued to said assignee, its successor, assigns and legal representatives, or to such nominees as it may designate.

We agree that, when requested, we will, without charge to said assignee but at its expense, sign all papers, take all rightful oaths, and do all acts which may be necessary, desirable or convenient for securing and maintaining Patents for said inventions in any and all countries and for vesting title thereto in said assignee, its successors, assigns and legal representatives or nominees.

We covenant with said assignee, its successors, assigns and legal representatives, that the rights and property herein conveyed are free and clear of any encumbrance, and that we have full right to convey the same as herein expressed.

We hereby authorize our attorney, J. ERIC THIES or an attorney with Power of Attorney in this application, of the said MERCK & CO., Inc., to insert **Serial No.**, and **Filing Date** of said application(s) when known.

Signed at RAHWAY, NEW JERSEY this 8th day of SEPTEMBER, 1995

Conrad P. Dorn
CONRAD P. DORN

Sander G. Mills
SANDER G. MILLS

Jeffrey J. Hale
JEFFREY J. HALE

Malcolm MacCoss
MALCOLM MACCOSS

PATENT
JOINT Merck Case 19189IA
U.S. Serial No. 08/525,870
Filing Date 9/8/95

ASSIGNMENT AND AGREEMENT

Signed at _____ this _____ day of _____.

_____

_____

_____

_____

STATE OF NEW JERSEY
County of UNION } SS.

Personally appeared before me the above-named CONRAD P. DORN JEFFREY J. HALE MALCOLM MACCOSS AND SANDER G. MILLS

to me known and known to me to be the person(s) who executed the foregoing instrument and acknowledged said instrument to be their free act and deed this 8th day of SEPTEMBER, 1995.

Robbin F. McCormick
Notary Public

ROBBIN F. McCORMICK
NOTARY PUBLIC OF NEW JERSEY
My Commission Expires March 21, 1999

_____
County of _____ } SS.

Personally appeared before me the above-named

to me known and known to me to be the person(s) who executed the foregoing instrument and acknowledged said instrument to be their free act and deed this _____ day of _____.

_____
Notary Public

EXHIBIT B

Power of Attorney

POWER OF ATTORNEY and CORRESPONDENCE ADDRESS INDICATION FORM

Application Number	08/525,870
Filing Date	September 8, 1995
First Named Inventor	Conrad P. Dorn et al.
Title	MORPHOLINE COMPOUNDS ARE PRODRUGS USEFUL AS TACHYKININ RECEPTOR ANTAGONISTS
Group Art Unit	1201
Examiner Name	F. Higel
Attorney Docket Number	19189IA

I hereby revoke all previous powers of attorney given in the above-identified application.

I hereby appoint:

☒ Practitioners associated with the Customer Number 000210

OR

☐ Practitioner(s) named below:

Name	Registration Number

as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.

Please recognize or change the correspondence address for the above-identified application to:

☒ The address associated with the above-mentioned Customer Number.

OR

☐ The address associated with Customer Number

OR

☒ Firm *or* Individual Name	Merck & Co., Inc.				
Address	P.O. Box 2000				
Address	126 East Lincoln Avenue				
City	Rahway	State	New Jersey	Zip	07065-0907
Country	USA				
Telephone		Fax	732-594-4720		

I am the:

☐ Applicant/Inventor.

☒ Assignee (s) of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed.

SIGNATURE of Applicant or Assignee of Record

Signature		Date	March 20, 2008
Name	William Krovatin	Telephone	732 594 0221
Title and Company	Managing Counsel, Patents, Merck & Co., Inc.		

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature required, see below*.

☐ *Total of _____ forms are submitted.

SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Merck & Co., Inc.

Application No./Patent No.: 5,691,336 Filed/Issue Date: November 25, 1997

Entitled: MORPHOLINE COMPOUNDS ARE PRODRUGS USEFUL AS TACHYKINN RECEPTOR ANTAGONISTS

Merck & Co., Inc., a Corporation,
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)
states that it is:

1. ☒ the assignee of the entire right, title, and interest; or

2. ☐ an assignee of less than the entire right, title and interest.
(The extent (by percentage) of its ownership interest is ____ %)

in the patent application/patent identified above by virtue of either:

A. ☒ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 8654 Frame 0863 ; Reel _____, Frame _____ ; Reel _____, Frame _____, or for which a copy thereof is attached.

OR

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

3. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet.

☐ As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.
[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Signature		Signature	
William Krovatin	March 20, 2008		
Printed or Typed Name	Date	Printed or Typed Name	Date
Managing Counsel, Patents	(732) 594-0221		
Title	Telephone Number	Title	Telephone Number

SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

General Corporate Resolution #5

PATENT MATTERS

RESOLVED, that any of the following:

Richard T. Clark–Chairman, Chief Executive Officer and President
Kenneth C. Frazier-Executive Vice President and General Counsel
Joseph F. DiPrima-Vice President and Assistant General Counsel
Paul D. Matukaitis-Vice President and Assistant General Counsel
Edward W. Murray-Managing Counsel, IP Litigation
Gerard Devlin-Counsel, IP Litigation
Valerie J. Camara-Managing Counsel, Patents
Mark R. Daniel-Managing Counsel, Patents
Catherine D. Fitch-Managing Counsel, Patents
Sheldon O. Heber-Managing Counsel, Patents
William Krovatin-Managing Counsel, Patents
David A. Muthard-Managing Counsel, Patents
Anthony Rollins-Managing Counsel, European Patents
Edward M. Yoshida-Managing Counsel, Rosetta Inpharmatics
Charles M. Caruso-Counsel, International
Peter Haeberli–Assistant Counsel, Sirna Therapeutics, Inc.
John Oksinski-Executive Director, Banyu
Kenichi Osawa–Senior Director, Banyu Patent and Trademark Group
Donna L. Margiotto-Senior Manager, Patent Administration

are authorized to execute and to revoke on behalf of Merck & Co., Inc. and its affiliates (including subsidiaries) the following documents relating to patent matters:

Powers of attorney as fully in law as may be necessary and proper in connection with the acquisition, registration, maintenance and enforcement of patents and applications for patents, including powers of attorney relating to the prosecution or defense of patent rights before courts of law or other governmental tribunals, agencies or departments; affidavits and declarations; and any other documents which are necessary and proper for the acquisition, registration, maintenance, litigation and protection of patents.

MERCK & CO. INC.

CERTIFICATION

I, Debra A. Bollwage, Senior Assistant Secretary of Merck & Co., Inc. (the "Company"), a corporation duly organized and existing under the laws of the State of New Jersey, do hereby certify that the attached, presently in full force and effect, is a true and correct copy of General Corporate Resolution #5, Patent Matters, as amended by Unanimous Written Consent of the Board of Directors of said Company on April 24, 2007.

IN WITNESS WHEREOF, I have hereunto subscribed my signature and affixed the seal of the Company this 27th day of April 2007.

Debra A. Bollwage
Senior Assistant Secretary

(SEAL)

EXHIBIT C

Letter from FDA Approving EMEND for Injection

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-023

NDA APPROVAL

Merck & Co., Inc.
Attention: Nicholas Andrew
Associate Director, Worldwide Regulatory Affairs
P.O. Box 2000, RY 33-200
Rahway, NJ 07065-0900

Dear Mr. Andrew:

Please refer to your new drug application (NDA) dated March 31, 2006, received April 3, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Emend (fosaprepitant dimeglumine) for Injection, 115 mg.

We acknowledge receipt of your submissions dated July 27, 2007; September 28, 2007; October 31, 2007; December 4, 2007; December 17, 2007; January 18, 2008; January 24, 2008; and January 25, 2008.

The July 27, 2007 submission constituted a complete response to our May 3, 2007 action letter.

This new drug application provides for the use of Emend (fosaprepitant dimeglumine) for Injection, 115 mg for:

- the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin.
- the prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert, text for the patient package insert). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 22-023."

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the submitted carton and immediate container labels dated January 25, 2008 as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22-023.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PEDIATRIC RESEARCH EQUITY ACT (PREA)

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for ages 0 months to <6 months because the necessary studies are impossible of highly impracticable because the number of pediatric cancer patients in this age group is so small. We are deferring pediatric studies for ages 6 months to 17 years for this application because adult studies have just been completed and additional pharmacokinetic information is needed.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of this postmarketing study shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. A study in adolescents and younger pediatric patients receiving emetogenic chemotherapy (HEC or MEC) to evaluate fosaprepitant PK, safety, and tolerability.

   Study Start Date: December 31, 2008
   Study Completion Date: March 31, 2011
   Final Report Submission: June 30, 2011

Submit final study reports to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment must be clearly designated "**Required Pediatric Study Commitments**".

POSTMARKETING COMMITMENTS

We remind you of your postmarketing study commitment in your submission dated January 24, 2008. This commitment is listed below.

2. Further characterize the effects of fosaprepitant on blood pressure.
   Statistical Plan Submission: by April 30, 2008
   Study Start: by April 30, 2008
   Final Report Submission: by July 31, 2008

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments should be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
HFD-001, Suite 5100
5515 Security Lane
Rockville, MD 20852

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Jagjit Grewal, Regulatory Project Manager, at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., MPH
Deputy Division Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Package Insert
Patient Package Insert

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joyce Korvick
1/25/2008 06:45:02 PM

EXHIBIT D

Approved Label for EMEND for Injection

MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

9840000

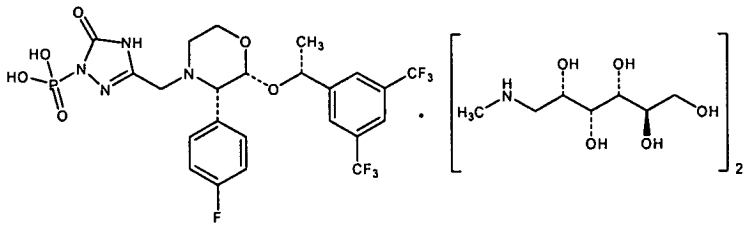
EMEND®

(fosaprepitant dimeglumine) for Injection

DESCRIPTION

EMEND[1] (fosaprepitant dimeglumine) for Injection is a sterile, lyophilized prodrug of aprepitant and is chemically described as 1-Deoxy-1-(methylamino)-D-glucitol[3-[[(2*R*,3*S*)-2-[(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-2,5-dihydro-5-oxo-1*H*-1,2,4-triazol-1-yl]phosphonate (2:1) (salt).

Its empirical formula is $C_{23}H_{22}F_7N_4O_6P \cdot 2(C_7H_{17}NO_5)$ and its structural formula is:



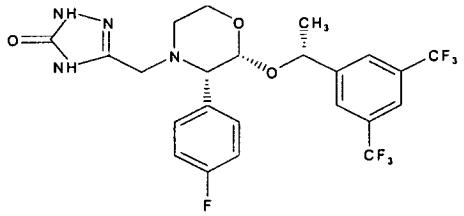
Fosaprepitant dimeglumine is a white to off-white amorphous powder with a molecular weight of 1004.83. It is freely soluble in water.

EMEND for Injection is a lyophilized prodrug of aprepitant containing polysorbate 80 (PS80), to be administered intravenously as an infusion.

Each vial of EMEND for Injection for intravenous administration contains 188 mg of fosaprepitant dimeglumine equivalent to 115 mg of fosaprepitant and the following inactive ingredients: edetate disodium (14.4 mg), polysorbate 80 (57.5 mg), lactose anhydrous (287.5 mg), sodium hydroxide and/or hydrochloric acid (for pH adjustment). Fosaprepitant dimeglumine hereafter will be referred to as fosaprepitant.

Aprepitant is a substance P/neurokinin 1 (NK_1) receptor antagonist, chemically described as 5-[[(2*R*,3*S*)-2-[(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3*H*-1,2,4-triazol-3-one.

Its empirical formula is $C_{23}H_{21}F_7N_4O_3$, and its structural formula is:



CLINICAL PHARMACOLOGY

Fosaprepitant, a prodrug of aprepitant, when administered intravenously is rapidly converted to aprepitant, a substance P/neurokinin 1 (NK1) receptor antagonist. Plasma concentrations of fosaprepitant are below the limits of quantification (10 ng/mL) within 30 minutes of the completion of infusion (see CLINICAL PHARMACOLOGY, *Pharmacokinetics*). Upon conversion of 115 mg of fosaprepitant to aprepitant, 18.3 mg of phosphate and 73 mg of meglumine are liberated from fosaprepitant.

---

[1]Trademark of MERCK & CO., Inc.

Mechanism of Action

Fosaprepitant is a prodrug of aprepitant and accordingly, its antiemetic effects are attributable to aprepitant.

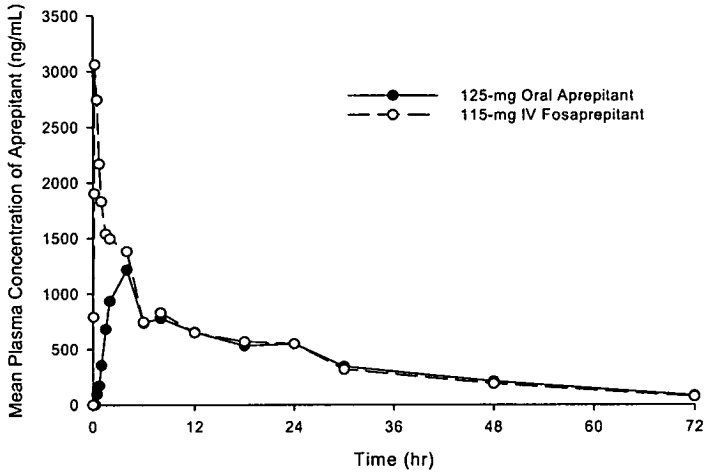
Aprepitant is a selective high-affinity antagonist of human substance P/neurokinin 1 (NK_1) receptors. Aprepitant has little or no affinity for serotonin ($5\text{-}HT_3$), dopamine, and corticosteroid receptors, the targets of existing therapies for chemotherapy-induced nausea and vomiting (CINV). Aprepitant has been shown in animal models to inhibit emesis induced by cytotoxic chemotherapeutic agents, such as cisplatin, via central actions. Animal and human Positron Emission Tomography (PET) studies with aprepitant have shown that it crosses the blood brain barrier and occupies brain NK_1 receptors. Animal and human studies show that aprepitant augments the antiemetic activity of the $5\text{-}HT_3$-receptor antagonist ondansetron and the corticosteroid dexamethasone and inhibits both the acute and delayed phases of cisplatin-induced emesis.

Pharmacokinetics

Aprepitant after Fosaprepitant Administration

Following a single intravenous dose of fosaprepitant administered as a 15-minute infusion to healthy volunteers the mean $AUC_{0-\infty}$ of aprepitant was 31.7 (± 14.3) mcg•hr/mL and the mean maximal aprepitant concentration (C_{max}) was 3.27 (± 1.16) mcg/mL. The mean aprepitant plasma concentration at 24 hours postdose was similar between the 125-mg oral aprepitant dose and the 115-mg intravenous fosaprepitant dose (See Figure 1).

Figure 1: Mean Plasma Concentration of Aprepitant
Following 125-mg Oral Aprepitant and 115-mg I.V. Fosaprepitant



Distribution

Fosaprepitant is rapidly converted to aprepitant. Aprepitant is greater than 95% bound to plasma proteins. The mean apparent volume of distribution at steady state (Vd_{ss}) is approximately 70 L in humans.

Aprepitant crosses the placenta in rats and rabbits and crosses the blood brain barrier in humans (see CLINICAL PHARMACOLOGY, *Mechanism of Action*).

Metabolism

Fosaprepitant was rapidly converted to aprepitant in *in vitro* incubations with liver preparations from nonclinical species (rat and dog) and humans. Furthermore, fosaprepitant underwent rapid and nearly complete conversion to aprepitant in S9 preparations from multiple other human tissues including kidney, lung and ileum. Thus, it appears that the conversion of fosaprepitant to aprepitant can occur in multiple extrahepatic tissues in addition to the liver. In humans, fosaprepitant administered intravenously was rapidly converted to aprepitant within 30 minutes following the end of infusion.

Aprepitant undergoes extensive metabolism. *In vitro* studies using human liver microsomes indicate that aprepitant is metabolized primarily by CYP3A4 with minor metabolism by CYP1A2 and CYP2C19. Metabolism is largely via oxidation at the morpholine ring and its side chains. No metabolism by CYP2D6,

CYP2C9, or CYP2E1 was detected. In healthy young adults, aprepitant accounts for approximately 24% of the radioactivity in plasma over 72 hours following a single oral 300-mg dose of [^{14}C]-aprepitant, indicating a substantial presence of metabolites in the plasma. Seven metabolites of aprepitant, which are only weakly active, have been identified in human plasma.

Excretion

Following administration of a single I.V. 100-mg dose of [^{14}C]-fosaprepitant to healthy subjects, 57% of the radioactivity was recovered in urine and 45% in feces.

Aprepitant is eliminated primarily by metabolism; aprepitant is not renally excreted. The apparent terminal half-life of aprepitant ranged from approximately 9 to 13 hours.

Special Populations

Fosaprepitant, a prodrug of aprepitant, when administered intravenously is rapidly converted to aprepitant.

Gender

Following oral administration of a single 125-mg dose of aprepitant, no difference in $AUC_{0\text{-}24hr}$ was observed between males and females. The C_{max} for aprepitant is 16% higher in females as compared with males. The half-life of aprepitant is 25% lower in females as compared with males and T_{max} occurs at approximately the same time. These differences are not considered clinically meaningful. No dosage adjustment is necessary based on gender.

Geriatric

Following oral administration of a single 125-mg dose of aprepitant on Day 1 and 80 mg once daily on Days 2 through 5, the $AUC_{0\text{-}24hr}$ of aprepitant was 21% higher on Day 1 and 36% higher on Day 5 in elderly (≥65 years) relative to younger adults. The C_{max} was 10% higher on Day 1 and 24% higher on Day 5 in elderly relative to younger adults. These differences are not considered clinically meaningful. No dosage adjustment is necessary in elderly patients.

Pediatric

Fosaprepitant has not been evaluated in patients below 18 years of age.

Race

Following oral administration of a single 125-mg dose of aprepitant, the $AUC_{0\text{-}24hr}$ is approximately 25% and 29% higher in Hispanics as compared with Whites and Blacks, respectively. The C_{max} is 22% and 31% higher in Hispanics as compared with Whites and Blacks, respectively. These differences are not considered clinically meaningful. There was no difference in $AUC_{0\text{-}24hr}$ or C_{max} between Whites and Blacks. No dosage adjustment is necessary based on race.

Hepatic Insufficiency

Fosaprepitant is metabolized in various extrahepatic tissues; therefore hepatic insufficiency is not expected to alter the conversion of fosaprepitant to aprepitant.

Oral aprepitant was well tolerated in patients with mild to moderate hepatic insufficiency. Following administration of a single 125-mg dose of oral aprepitant on Day 1 and 80 mg once daily on Days 2 and 3 to patients with mild hepatic insufficiency (Child-Pugh score 5 to 6), the $AUC_{0\text{-}24hr}$ of aprepitant was 11% lower on Day 1 and 36% lower on Day 3, as compared with healthy subjects given the same regimen. In patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), the $AUC_{0\text{-}24hr}$ of aprepitant was 10% higher on Day 1 and 18% higher on Day 3, as compared with healthy subjects given the same regimen. These differences in $AUC_{0\text{-}24hr}$ are not considered clinically meaningful; therefore, no dosage adjustment is necessary in patients with mild to moderate hepatic insufficiency.

There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score >9) (see PRECAUTIONS).

Renal Insufficiency

A single 240-mg dose of oral aprepitant was administered to patients with severe renal insufficiency (CrCl<30 mL/min) and to patients with end stage renal disease (ESRD) requiring hemodialysis.

In patients with severe renal insufficiency, the $AUC_{0\text{-}\infty}$ of total aprepitant (unbound and protein bound) decreased by 21% and C_{max} decreased by 32%, relative to healthy subjects. In patients with ESRD undergoing hemodialysis, the $AUC_{0\text{-}\infty}$ of total aprepitant decreased by 42% and C_{max} decreased by 32%. Due to modest decreases in protein binding of aprepitant in patients with renal disease, the AUC of pharmacologically active unbound drug was not significantly affected in patients with renal insufficiency compared with healthy subjects. Hemodialysis conducted 4 or 48 hours after dosing had no significant effect on the pharmacokinetics of aprepitant; less than 0.2% of the dose was recovered in the dialysate.

No dosage adjustment is necessary for patients with renal insufficiency or for patients with ESRD undergoing hemodialysis.

Pharmacodynamics
Cardiac Electrophysiology
In a randomized, double-blind, positive-controlled, thorough QTc study, a single 200-mg dose of fosaprepitant had no effect on the QTc interval.
Clinical Studies
Fosaprepitant, a prodrug of aprepitant, when administered intravenously is rapidly converted to aprepitant. Fosaprepitant 115 mg I.V. infused over 15 minutes can be substituted for 125 mg oral aprepitant on Day 1 (see DOSAGE AND ADMINISTRATION). Pivotal efficacy studies were conducted with oral aprepitant.
Oral administration of aprepitant in combination with ondansetron and dexamethasone (aprepitant regimen) has been shown to prevent acute and delayed nausea and vomiting associated with highly emetogenic chemotherapy including high-dose cisplatin, and nausea and vomiting associated with moderately emetogenic chemotherapy.
Highly Emetogenic Chemotherapy
In 2 multicenter, randomized, parallel, double-blind, controlled clinical studies, the aprepitant regimen (see table below) was compared with standard therapy in patients receiving a chemotherapy regimen that included cisplatin >50 mg/m^2 (mean cisplatin dose = 80.2 mg/m^2). Of the 550 patients who were randomized to receive the aprepitant regimen, 42% were women, 58% men, 59% White, 3% Asian, 5% Black, 12% Hispanic American, and 21% Multi-Racial. The aprepitant-treated patients in these clinical studies ranged from 14 to 84 years of age, with a mean age of 56 years. 170 patients were 65 years or older, with 29 patients being 75 years or older.
Patients (N = 1105) were randomized to either the aprepitant regimen (N = 550) or standard therapy (N = 555). The treatment regimens are defined in the table below.

Treatment Regimens
Highly Emetogenic Chemotherapy Trials

Treatment Regimen	Day 1	Days 2 to 4
Aprepitant	Aprepitant 125 mg PO Dexamethasone 12 mg PO Ondansetron 32 mg I.V .	Aprepitant 80 mg PO Daily (Days 2 and 3 only) Dexamethasone 8 mg PO Daily (morning)
Standard Therapy	Dexamethasone 20 mg PO Ondansetron 32 mg I.V .	Dexamethasone 8 mg PO Daily (morning) Dexamethasone 8 mg PO Daily (evening)

Aprepitant placebo and dexamethasone placebo were used to maintain blinding.

During these studies 95% of the patients in the aprepitant group received a concomitant chemotherapeutic agent in addition to protocol-mandated cisplatin. The most common chemotherapeutic agents and the number of aprepitant patients exposed follow: etoposide (106), fluorouracil (100), gemcitabine (89), vinorelbine (82), paclitaxel (52), cyclophosphamide (50), doxorubicin (38), docetaxel (11).
The antiemetic activity of oral aprepitant was evaluated during the acute phase (0 to 24 hours post-cisplatin treatment), the delayed phase (25 to 120 hours post-cisplatin treatment) and overall (0 to 120 hours post-cisplatin treatment) in Cycle 1. Efficacy was based on evaluation of the following endpoints:
Primary endpoint:
- complete response (defined as no emetic episodes and no use of rescue therapy)

Other prespecified endpoints:
- complete protection (defined as no emetic episodes, no use of rescue therapy, and a maximum nausea visual analogue scale [VAS] score <25 mm on a 0 to 100 mm scale)
- no emesis (defined as no emetic episodes regardless of use of rescue therapy)
- no nausea (maximum VAS <5 mm on a 0 to 100 mm scale)
- no significant nausea (maximum VAS <25 mm on a 0 to 100 mm scale)

A summary of the key study results from each individual study analysis is shown in Table 1 and in Table 2.

Table 1

Percent of Patients Receiving Highly Emetogenic Chemotherapy Responding by Treatment Group and Phase for Study 1 — Cycle 1

ENDPOINTS	Aprepitant Regimen (N = 260)† %	Standard Therapy (N = 261)† %	p-Value
PRIMARY ENDPOINT			
Complete Response			
Overall‡	73	52	<0.001
OTHER PRESPECIFIED ENDPOINTS			
Complete Response			
Acute phase§	89	78	<0.001
Delayed phase‖	75	56	<0.001
Complete Protection			
Overall	63	49	0.001
Acute phase	85	75	NS*
Delayed phase	66	52	<0.001
No Emesis			
Overall	78	55	<0.001
Acute phase	90	79	0.001
Delayed phase	81	59	<0.001
No Nausea			
Overall	48	44	NS**
Delayed phase	51	48	NS**
No Significant Nausea			
Overall	73	66	NS**
Delayed phase	75	69	NS**

†N: Number of patients (older than 18 years of age) who received cisplatin, study drug, and had at least one post-treatment efficacy evaluation.
‡Overall: 0 to 120 hours post-cisplatin treatment.
§Acute phase: 0 to 24 hours post-cisplatin treatment.
‖Delayed phase: 25 to 120 hours post-cisplatin treatment.
*Not statistically significant when adjusted for multiple comparisons.
**Not statistically significant.
Visual analogue scale (VAS) score range: 0 mm = no nausea; 100 mm = nausea as bad as it could be.

Table 2

Percent of Patients Receiving Highly Emetogenic Chemotherapy Responding by Treatment Group and Phase for Study 2 — Cycle 1

ENDPOINTS	Aprepitant Regimen (N = 261)† %	Standard Therapy (N = 263)† %	p-Value
PRIMARY ENDPOINT			
Complete Response			
Overall‡	63	43	<0.001
OTHER PRESPECIFIED ENDPOINTS			
Complete Response			
Acute phase§	83	68	<0.001
Delayed phase‖	68	47	<0.001
Complete Protection			
Overall	56	41	<0.001
Acute phase	80	65	<0.001
Delayed phase	61	44	<0.001
No Emesis			
Overall	66	44	<0.001
Acute phase	84	69	<0.001
Delayed phase	72	48	<0.001
No Nausea			
Overall	49	39	NS*
Delayed phase	53	40	NS*
No Significant Nausea			
Overall	71	64	NS**
Delayed phase	73	65	NS**

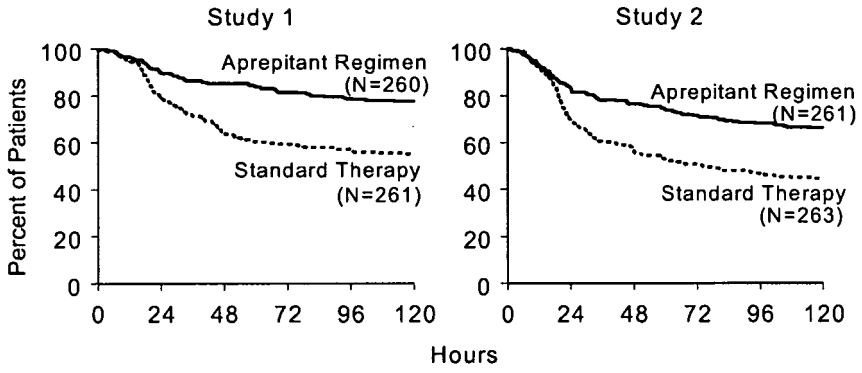
†N: Number of patients (older than 18 years of age) who received cisplatin, study drug, and had at least one post-treatment efficacy evaluation.
‡Overall: 0 to 120 hours post-cisplatin treatment.
§Acute phase: 0 to 24 hours post-cisplatin treatment.

[‖]Delayed phase: 25 to 120 hours post-cisplatin treatment.
*Not statistically significant when adjusted for multiple comparisons.
**Not statistically significant.
Visual analogue scale (VAS) score range: 0 mm = no nausea; 100 mm = nausea as bad as it could be.

In both studies, a statistically significantly higher proportion of patients receiving the aprepitant regimen in Cycle 1 had a complete response (primary endpoint), compared with patients receiving standard therapy. A statistically significant difference in complete response in favor of the aprepitant regimen was also observed when the acute phase and the delayed phase were analyzed separately.

In both studies, the estimated time to first emesis after initiation of cisplatin treatment was longer with the aprepitant regimen, and the incidence of first emesis was reduced in the aprepitant regimen group compared with standard therapy group as depicted in the Kaplan-Meier curves in Figure 2.

Figure 2: Percent of Patients Receiving Highly Emetogenic Chemotherapy Who Remain Emesis Free Over Time – Cycle 1

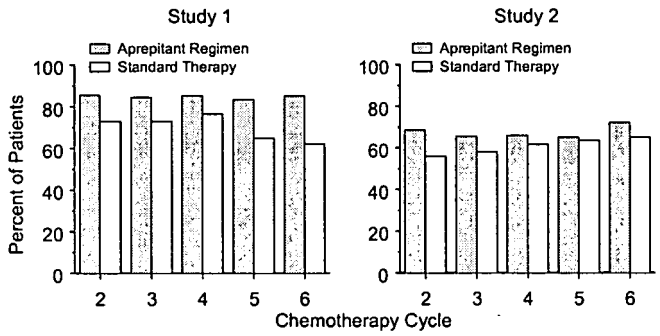


p-Value <0.001 based on a log rank test for Study 1 and Study 2; nominal p-values not adjusted for multiplicity.

Patient-Reported Outcomes: The impact of nausea and vomiting on patients' daily lives was assessed in Cycle 1 of both Phase III studies using the Functional Living Index–Emesis (FLIE), a validated nausea- and vomiting-specific patient-reported outcome measure. Minimal or no impact of nausea and vomiting on patients' daily lives is defined as a FLIE total score >108. In each of the 2 studies, a higher proportion of patients receiving the aprepitant regimen reported minimal or no impact of nausea and vomiting on daily life (Study 1: 74% versus 64%; Study 2: 75% versus 64%).

Multiple-Cycle Extension: In the same 2 clinical studies, patients continued into the Multiple-Cycle extension for up to 5 additional cycles of chemotherapy. The proportion of patients with no emesis and no significant nausea by treatment group at each cycle is depicted in Figure 3. Antiemetic effectiveness for the patients receiving the aprepitant regimen is maintained throughout repeat cycles for those patients continuing in each of the multiple cycles.

Figure 3: Proportion of Patients Receiving Highly Emetogenic Chemotherapy With No Emesis and No Significant Nausea by Treatment Group and Cycle



	Study 1					Study 2				
Aprepitant (N)	158	122	81	54	40	191	148	103	63	43
Standard (N)	177	111	68	37	29	216	167	112	74	43

Moderately Emetogenic Chemotherapy

In a multicenter, randomized, double-blind, parallel-group, clinical study in breast cancer patients, the aprepitant regimen (see table that follows) was compared with a standard of care therapy in patients receiving a moderately emetogenic chemotherapy regimen that included cyclophosphamide 750-1500 mg/m^2; or cyclophosphamide 500-1500 mg/m^2 and doxorubicin (≤60 mg/m^2) or epirubicin (≤100 mg/m^2).

In this study, the most common combinations were cyclophosphamide + doxorubicin (60.6%); and cyclophosphamide + epirubicin + fluorouracil (21.6%).

Of the 438 patients who were randomized to receive the aprepitant regimen, 99.5% were women. Of these, approximately 80% were White, 8% Black, 8% Asian, 4% Hispanic, and <1% Other. The aprepitant-treated patients in this clinical study ranged from 25 to 78 years of age, with a mean age of 53 years; 70 patients were 65 years or older, with 12 patients being over 74 years.

Patients (N = 866) were randomized to either the aprepitant regimen (N = 438) or standard therapy (N = 428). The treatment regimens are defined in the table that follows.

Treatment Regimens
Moderately Emetogenic Chemotherapy Trial

Treatment Regimen	Day 1	Days 2 to 3
Aprepitant	Aprepitant 125 mg PO[†] Dexamethasone 12 mg PO[‡] Ondansetron 8 mg PO x 2 doses[§]	Aprepitant 80 mg PO Daily
Standard Therapy	Dexamethasone 20 mg PO Ondansetron 8 mg PO x 2 doses	Ondansetron 8 mg PO Daily (every 12 hours)

Aprepitant placebo and dexamethasone placebo were used to maintain blinding.
[†]1 hour prior to chemotherapy.
[‡]30 minutes prior to chemotherapy.
[§]30 to 60 minutes prior to chemotherapy and 8 hours after first ondansetron dose.

The antiemetic activity of oral aprepitant was evaluated based on the following endpoints:

Primary endpoint:

Complete response (defined as no emetic episodes and no use of rescue therapy) in the overall phase (0 to 120 hours post-chemotherapy)

Other prespecified endpoints:

- no emesis (defined as no emetic episodes regardless of use of rescue therapy)
- no nausea (maximum VAS <5 mm on a 0 to 100 mm scale)
- no significant nausea (maximum VAS <25 mm on a 0 to 100 mm scale)
- complete protection (defined as no emetic episodes, no use of rescue therapy, and a maximum nausea visual analogue scale [VAS] score <25 mm on a 0 to 100 mm scale)
- complete response during the acute and delayed phases.

A summary of the key results from this study is shown in Table 3.

Table 3

Percent of Patients Receiving Moderately Emetogenic Chemotherapy Responding by Treatment Group and Phase — Cycle 1

ENDPOINTS	Aprepitant Regimen (N = 433)[†] %	Standard Therapy (N = 424)[†] %	p-Value
PRIMARY ENDPOINT			
Complete Response[‡]	51	42	0.015
OTHER PRESPECIFIED ENDPOINTS			
No Emesis	76	59	NS*
No Nausea	33	33	NS
No Significant Nausea	61	56	NS
No Rescue Therapy	59	56	NS
Complete Protection	43	37	NS

[†]N: Number of patients included in the primary analysis of complete response.

‡Overall: 0 to 120 hours post-chemotherapy treatment.
*NS when adjusted for prespecified multiple comparisons rule; unadjusted p-value <0.001.

In this study, a statistically significantly (p=0.015) higher proportion of patients receiving the aprepitant regimen (51%) in Cycle 1 had a complete response (primary endpoint) during the overall phase compared with patients receiving standard therapy (42%). The difference between treatment groups was primarily driven by the "No Emesis Endpoint", a principal component of this composite primary endpoint. In addition, a higher proportion of patients receiving the aprepitant regimen in Cycle 1 had a complete response during the acute (0-24 hours) and delayed (25-120 hours) phases compared with patients receiving standard therapy; however, the treatment group differences failed to reach statistical significance, after multiplicity adjustments.

Patient-Reported Outcomes: In a phase III study in patients receiving moderately emetogenic chemotherapy, the impact of nausea and vomiting on patients' daily lives was assessed in Cycle 1 using the FLIE. A higher proportion of patients receiving the aprepitant regimen reported minimal or no impact on daily life (64% versus 56%). This difference between treatment groups was primarily driven by the "No Vomiting Domain" of this composite endpoint.

Multiple-Cycle Extension: Patients receiving moderately emetogenic chemotherapy were permitted to continue into the Multiple-Cycle extension of the study for up to 3 additional cycles of chemotherapy. Antiemetic effect for patients receiving the aprepitant regimen is maintained during all cycles.

INDICATIONS AND USAGE

EMEND for Injection, in combination with other antiemetic agents, is indicated for the:

- prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy including high-dose cisplatin
- prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

EMEND for Injection is contraindicated in patients who are hypersensitive to EMEND for Injection, aprepitant, polysorbate 80 or any other components of the product.

Aprepitant, when administered orally, is a moderate cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitor following the 3-day antiemetic dosing regimen for CINV. Since fosaprepitant is rapidly converted to aprepitant, fosaprepitant should not be used concurrently with pimozide, terfenadine, astemizole, or cisapride. Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions (see PRECAUTIONS, *Drug Interactions*).

PRECAUTIONS

General

Fosaprepitant is rapidly converted to aprepitant, which is a moderate inhibitor of CYP3A4 when administered as a 3-day antiemetic dosing regimen for CINV. Fosaprepitant should be used with caution in patients receiving concomitant medications that are primarily metabolized through CYP3A4. Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these concomitant medications. When fosaprepitant is used concomitantly with another CYP3A4 inhibitor, aprepitant plasma concentrations could be elevated. (See PRECAUTIONS; *Drug Interactions*.)

Chemotherapy agents that are known to be metabolized by CYP3A4 include docetaxel, paclitaxel, etoposide, irinotecan, ifosfamide, imatinib, vinorelbine, vinblastine and vincristine. In clinical studies, the oral aprepitant regimen was administered commonly with etoposide, vinorelbine, or paclitaxel. The doses of these agents were not adjusted to account for potential drug interactions.

In separate pharmacokinetic studies no clinically significant change in docetaxel or vinorelbine pharmacokinetics was observed when the oral aprepitant regimen was co-administered.

Due to the small number of patients in clinical studies who received the CYP3A4 substrates vinblastine, vincristine, or ifosfamide, particular caution and careful monitoring are advised in patients receiving these agents or other chemotherapy agents metabolized primarily by CYP3A4 that were not studied (see PRECAUTIONS, *Drug Interactions*).

Chronic continuous use of EMEND for Injection for prevention of nausea and vomiting is not recommended because it has not been studied and because the drug interaction profile may change during chronic continuous use.

Coadministration of aprepitant with warfarin may result in a clinically significant decrease in International Normalized Ratio (INR) of prothrombin time. In patients on chronic warfarin therapy, the INR should be closely monitored in the 2-week period, particularly at 7 to 10 days, following initiation of the 3-day regimen of fosaprepitant followed by oral aprepitant with each chemotherapy cycle (see PRECAUTIONS, *Drug Interactions*).

Upon coadministration with aprepitant, the efficacy of hormonal contraceptives during and for 28 days following the last dose of aprepitant may be reduced. Alternative or back-up methods of contraception should be used during treatment with aprepitant and for 1 month following the last dose of aprepitant (see PRECAUTIONS, *Drug Interactions*).

There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score >9). Therefore, caution should be exercised when fosaprepitant or aprepitant is administered in these patients (see CLINICAL PHARMACOLOGY, *Special Populations, Hepatic Insufficiency* and DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians should instruct their patients to read the patient package insert before starting therapy with EMEND for Injection and to reread it each time the prescription is renewed.

Patients should follow the physician's instructions for the EMEND for Injection regimen.

For the prevention of CINV, patients should be given their dose of EMEND for Injection as an infusion over 15 minutes, 30 minutes prior to chemotherapy on Day 1.

EMEND for Injection may interact with some drugs including chemotherapy; therefore, patients should be advised to report to their doctor the use of any other prescription, non-prescription medication or herbal products.

Patients on chronic warfarin therapy should be instructed to have their clotting status closely monitored in the 2-week period, particularly at 7 to 10 days, following initiation of the 3-day regimen of fosaprepitant followed by aprepitant, with each chemotherapy cycle.

Administration of EMEND for Injection may reduce the efficacy of hormonal contraceptives. Patients should be advised to use alternative or back-up methods of contraception during treatment with EMEND for Injection and for 1 month following the last dose of the 3-day aprepitant regimen.

Drug Interactions

Drug interactions following administration of fosaprepitant are likely to occur with drugs that interact with oral aprepitant. The following information was derived from data with oral aprepitant and one study conducted with fosaprepitant and oral midazolam.

Aprepitant is a substrate, a moderate inhibitor, and an inducer of CYP3A4 when administered as a 3-day antiemetic dosing regimen for CINV. Aprepitant is also an inducer of CYP2C9.

Effect of aprepitant on the pharmacokinetics of other agents

As a moderate inhibitor of CYP3A4, aprepitant can increase plasma concentrations of orally coadministered medicinal products that are metabolized through CYP3A4 (see CONTRAINDICATIONS).

Aprepitant has been shown to induce the metabolism of S(-) warfarin and tolbutamide, which are metabolized through CYP2C9. Coadministration of fosaprepitant or oral aprepitant with these drugs or other drugs that are known to be metabolized by CYP2C9, such as phenytoin, may result in lower plasma concentrations of these drugs.

Fosaprepitant or aprepitant is unlikely to interact with drugs that are substrates for the P-glycoprotein transporter, as demonstrated by the lack of interaction of oral aprepitant with digoxin in a clinical drug interaction study.

5-HT_3 antagonists: In clinical drug interaction studies, aprepitant did not have clinically important effects on the pharmacokinetics of ondansetron, granisetron, or hydrodolasetron (the active metabolite of dolasetron).

Corticosteroids:

Dexamethasone: Oral aprepitant, when given as a regimen of 125 mg with dexamethasone coadministered orally as 20 mg on Day 1, and oral aprepitant when given as 80 mg/day with dexamethasone coadministered orally as 8 mg on Days 2 through 5, increased the AUC of dexamethasone, a CYP3A4 substrate, by 2.2-fold on Days 1 and 5. The oral dexamethasone doses should be reduced by approximately 50% when coadministered with a regimen of fosaprepitant followed by aprepitant, to achieve exposures of dexamethasone similar to those obtained when dexamethasone is

given without aprepitant. The daily dose of dexamethasone administered in clinical CINV studies with oral aprepitant reflects an approximate 50% reduction of the dose of dexamethasone (see DOSAGE AND ADMINISTRATION).

Methylprednisolone: Oral aprepitant, when given as a regimen of 125 mg on Day 1 and 80 mg/day on Days 2 and 3, increased the AUC of methylprednisolone, a CYP3A4 substrate, by 1.34-fold on Day 1 and by 2.5-fold on Day 3, when methylprednisolone was coadministered intravenously as 125 mg on Day 1 and orally as 40 mg on Days 2 and 3. The I.V. methylprednisolone dose should be reduced by approximately 25%, and the oral methylprednisolone dose should be reduced by approximately 50% when coadministered with a regimen of fosaprepitant followed by aprepitant to achieve exposures of methylprednisolone similar to those obtained when it is given without aprepitant.

Chemotherapeutic agents: See PRECAUTIONS, *General.*

Docetaxel: In a pharmacokinetic study, oral aprepitant (CINV regimen) did not influence the pharmacokinetics of docetaxel.

Vinorelbine: In a pharmacokinetic study, oral aprepitant (CINV regimen) did not influence the pharmacokinetics of vinorelbine to a clinically significant degree.

Warfarin: A single 125-mg dose of oral aprepitant was administered on Day 1 and 80 mg/day on Days 2 and 3 to healthy subjects who were stabilized on chronic warfarin therapy. Although there was no effect of oral aprepitant on the plasma AUC of R(+) or S(-) warfarin determined on Day 3, there was a 34% decrease in S(-) warfarin (a CYP2C9 substrate) trough concentration accompanied by a 14% decrease in the prothrombin time (reported as International Normalized Ratio or INR) 5 days after completion of dosing with oral aprepitant. In patients on chronic warfarin therapy, the prothrombin time (INR) should be closely monitored in the 2-week period, particularly at 7 to 10 days, following initiation of the 3-day regimen of fosaprepitant followed by aprepitant with each chemotherapy cycle.

Tolbutamide: Oral aprepitant, when given as 125 mg on Day 1 and 80 mg/day on Days 2 and 3, decreased the AUC of tolbutamide (a CYP2C9 substrate) by 23% on Day 4, 28% on Day 8, and 15% on Day 15, when a single dose of tolbutamide 500 mg was administered orally prior to the administration of the 3-day regimen of oral aprepitant and on Days 4, 8, and 15.

Oral contraceptives: Aprepitant, when given once daily for 14 days as a 100-mg capsule with an oral contraceptive containing 35 mcg of ethinyl estradiol and 1 mg of norethindrone, decreased the AUC of ethinyl estradiol by 43%, and decreased the AUC of norethindrone by 8%.

In another study, a daily dose of an oral contraceptive containing ethinyl estradiol and norethindrone was administered on Days 1 through 21, and oral aprepitant was given as a 3-day regimen of 125 mg on Day 8 and 80 mg/day on Days 9 and 10 with ondansetron 32 mg I.V. on Day 8 and oral dexamethasone given as 12 mg on Day 8 and 8 mg/day on Days 9, 10, and 11. In the study, the AUC of ethinyl estradiol decreased by 19% on Day 10 and there was as much as a 64% decrease in ethinyl estradiol trough concentrations during Days 9 through 21. While there was no effect of oral aprepitant on the AUC of norethindrone on Day 10, there was as much as a 60% decrease in norethindrone trough concentrations during Days 9 through 21. The coadministration of fosaprepitant or aprepitant may reduce the efficacy of hormonal contraceptives during and for 28 days after administration of the last dose of either. Alternative or back-up methods of contraception should be used during treatment with fosaprepitant or aprepitant and for 1 month following the last dose.

Midazolam: A study was completed with fosaprepitant and oral midazolam. Fosaprepitant was given at a dose of 100 mg over 15 minutes along with a single dose of midazolam 2 mg. The plasma AUC of midazolam was increased by 1.6-fold. This effect was not considered clinically important.

Oral aprepitant increased the AUC of midazolam by 2.3-fold on Day 1 and 3.3-fold on Day 5, when a single oral dose of midazolam 2 mg was coadministered on Day 1 and Day 5 of a regimen of oral aprepitant 125 mg on Day 1 and 80 mg/day on Days 2 through 5. The potential effects of increased plasma concentrations of midazolam or other benzodiazepines metabolized via CYP3A4 (alprazolam, triazolam) should be considered when coadministering these agents with a 3-day regimen of fosaprepitant followed by aprepitant. In another study with intravenous administration of midazolam, oral aprepitant was given as 125 mg on Day 1 and 80 mg/day on Days 2 and 3, and midazolam 2 mg I.V. was given prior to the administration of the 3-day regimen of oral aprepitant and on Days 4, 8, and 15. Oral aprepitant increased the AUC of midazolam by 25% on Day 4 and decreased the AUC of midazolam by 19% on Day 8 relative to the dosing of oral aprepitant on Days 1 through 3. These effects were not considered clinically important. The AUC of midazolam on Day 15 was similar to that observed at baseline.

An additional study was completed with intravenous administration of midazolam and oral aprepitant. Intravenous midazolam 2 mg was given 1 hour after oral administration of a single dose of oral aprepitant 125 mg. The plasma AUC of midazolam was increased by 1.5-fold.

Effect of other agents on the pharmacokinetics of aprepitant

Aprepitant is a substrate for CYP3A4; therefore, coadministration of fosaprepitant or aprepitant with drugs that inhibit CYP3A4 activity may result in increased plasma concentrations of aprepitant. Consequently, concomitant administration of fosaprepitant or aprepitant with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, nelfinavir) should be approached with caution. Because moderate CYP3A4 inhibitors (e.g., diltiazem) result in a 2-fold increase in plasma concentrations of aprepitant, concomitant administration should also be approached with caution.

Aprepitant is a substrate for CYP3A4; therefore, coadministration of fosaprepitant or aprepitant with drugs that strongly induce CYP3A4 activity (e.g., rifampin, carbamazepine, phenytoin) may result in reduced plasma concentrations and decreased efficacy.

Ketoconazole: When a single 125-mg dose of oral aprepitant was administered on Day 5 of a 10-day regimen of 400 mg/day of ketoconazole, a strong CYP3A4 inhibitor, the AUC of aprepitant increased approximately 5-fold and the mean terminal half-life of aprepitant increased approximately 3-fold. Concomitant administration of fosaprepitant or aprepitant with strong CYP3A4 inhibitors should be approached cautiously.

Rifampin: When a single 375-mg dose of oral aprepitant was administered on Day 9 of a 14-day regimen of 600 mg/day of rifampin, a strong CYP3A4 inducer, the AUC of aprepitant decreased approximately 11-fold and the mean terminal half-life decreased approximately 3-fold.

Coadministration of fosaprepitant or aprepitant with drugs that induce CYP3A4 activity may result in reduced plasma concentrations and decreased efficacy.

Additional interactions

Diltiazem: In a study in 10 patients with mild to moderate hypertension, intravenous infusion of 100 mg fosaprepitant over 15 minutes with diltiazem 120 mg 3 times daily, resulted in a 1.5-fold increase of aprepitant AUC and a 1.4-fold increase in diltiazem AUC. It also resulted in a small but clinically meaningful further maximum decrease in diastolic blood pressure [mean (SD) of 24.3 (± 10.2) mm Hg with fosaprepitant versus 15.6 (± 4.1) mm Hg without fosaprepitant] and resulted in a small further maximum decrease in systolic blood pressure [mean (SD) of 29.5 (± 7.9) mm Hg with fosaprepitant versus 23.8 (± 4.8) mm Hg without fosaprepitant], which may be clinically meaningful, but did not result in a clinically meaningful further change in heart rate or PR interval, beyond those changes induced by diltiazem alone.

In the same study, administration of aprepitant once daily, as a tablet formulation comparable to 230 mg of the capsule formulation, with diltiazem 120 mg 3 times daily for 5 days, resulted in a 2-fold increase of aprepitant AUC and a simultaneous 1.7-fold increase of diltiazem AUC. These pharmacokinetic effects did not result in clinically meaningful changes in ECG, heart rate or blood pressure beyond those changes induced by diltiazem alone.

Paroxetine: Coadministration of once daily doses of aprepitant, as a tablet formulation comparable to 85 mg or 170 mg of the capsule formulation, with paroxetine 20 mg once daily, resulted in a decrease in AUC by approximately 25% and C_{max} by approximately 20% of both aprepitant and paroxetine.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies were conducted in Sprague-Dawley rats and in CD-1 mice for 2 years. In the rat carcinogenicity studies, animals were treated with oral doses ranging from 0.05 to 1000 mg/kg twice daily. The highest dose produced a systemic exposure to aprepitant (plasma $AUC_{0\text{-}24hr}$) of 0.7 to 1.6 times the human exposure ($AUC_{0\text{-}24hr}$ = 19.6 mcg•hr/mL) at the recommended dose of 125 mg/day. Treatment with aprepitant at doses of 5 to 1000 mg/kg twice daily caused an increase in the incidences of thyroid follicular cell adenomas and carcinomas in male rats. In female rats, it produced hepatocellular adenomas at 5 to 1000 mg/kg twice daily and hepatocellular carcinomas and thyroid follicular cell adenomas at 125 to 1000 mg/kg twice daily. In the mouse carcinogenicity studies, the animals were treated with oral doses ranging from 2.5 to 2000 mg/kg/day. The highest dose produced a systemic exposure of about 2.8 to 3.6 times the human exposure at the recommended dose. Treatment with aprepitant produced skin fibrosarcomas at 125 and 500 mg/kg/day doses in male mice. Carcinogenicity studies were not conducted with fosaprepitant.

Aprepitant and fosaprepitant were not genotoxic in the Ames test, the human lymphoblastoid cell (TK6) mutagenesis test, the rat hepatocyte DNA strand break test, the Chinese hamster ovary (CHO) cell chromosome aberration test and the mouse micronucleus test.

Fosaprepitant, when administered intravenously, is rapidly converted to aprepitant. In the fertility studies conducted with fosaprepitant and aprepitant, the highest systemic exposures to aprepitant were obtained following oral administration of aprepitant. Oral aprepitant did not affect the fertility or general reproductive performance of male or female rats at doses up to the maximum feasible dose of 1000 mg/kg twice daily (providing exposure in male rats lower than the exposure at the recommended human dose and exposure in female rats at about 1.6 times the human exposure).

Pregnancy. Teratogenic Effects: Category B. In the teratology studies conducted with fosaprepitant and aprepitant, the highest systemic exposures to aprepitant were obtained following oral administration of aprepitant. Teratology studies performed in rats at oral doses of aprepitant up to 1000 mg/kg twice daily (plasma $AUC_{0\text{-}24hr}$ of 31.3 mcg•hr/mL, about 1.6 times the human exposure at the recommended dose) and in rabbits at oral doses up to 25 mg/kg/day (plasma $AUC_{0\text{-}24hr}$ of 26.9 mcg•hr/mL, about 1.4 times the human exposure at the recommended dose) revealed no evidence of impaired fertility or harm to the fetus due to aprepitant. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Aprepitant is excreted in the milk of rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for possible serious adverse reactions in nursing infants from aprepitant and because of the potential for tumorigenicity shown for aprepitant in rodent carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

In 2 well-controlled chemotherapy-induced nausea and vomiting clinical studies, of the total number of patients (N=544) treated with oral aprepitant, 31% were 65 and over, while 5% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Greater sensitivity of some older individuals cannot be ruled out. Dosage adjustment in the elderly is not necessary.

ADVERSE REACTIONS

The overall safety of aprepitant was evaluated in approximately 4900 individuals.

Since EMEND for Injection is converted to aprepitant, those adverse experiences associated with aprepitant might also be expected to occur with EMEND for Injection.

Fosaprepitant (intravenous formulation)

In a randomized, open-label, incomplete crossover, bioequivalence study, 66 subjects were dosed with 115 mg of EMEND for Injection intravenously and 72 subjects received 125 mg of aprepitant orally. Systemic exposure of 115 mg of intravenous EMEND for Injection is equivalent to 125 mg oral aprepitant. The following clinical adverse experiences, regardless of causality, were reported in subjects dosed with EMEND for Injection: infusion site pain, 5 (7.6%); infusion site induration, 1(1.5%); headache, 2(3%).

Oral Aprepitant

Highly Emetogenic Chemotherapy

In 2 well-controlled clinical trials in patients receiving highly emetogenic cancer chemotherapy, 544 patients were treated with aprepitant during Cycle 1 of chemotherapy and 413 of these patients continued into the Multiple-Cycle extension for up to 6 cycles of chemotherapy. Oral aprepitant was given in combination with ondansetron and dexamethasone and was generally well tolerated. Most adverse experiences reported in these clinical studies were described as mild to moderate in intensity.

In Cycle 1, clinical adverse experiences were reported in approximately 69% of patients treated with the aprepitant regimen compared with approximately 68% of patients treated with standard therapy. Table 4 shows the percent of patients with clinical adverse experiences reported at an incidence ≥3%.

Table 4

Percent of Patients Receiving Highly Emetogenic Chemotherapy With Clinical Adverse Experiences (Incidence ≥3%) - Cycle 1

	Aprepitant Regimen (N = 544)	Standard Therapy (N = 550)
Body as a Whole/ Site Unspecified		
Abdominal Pain	4.6	3.3
Asthenia/Fatigue	17.8	11.8
Dehydration	5.9	5.1
Dizziness	6.6	4.4
Fever	2.9	3.5
Mucous Membrane Disorder	2.6	3.1
Digestive System		
Constipation	10.3	12.2
Diarrhea	10.3	7.5
Epigastric Discomfort	4.0	3.1
Gastritis	4.2	3.1
Heartburn	5.3	4.9
Nausea	12.7	11.8
Vomiting	7.5	7.6
Eyes, Ears, Nose, and Throat		
Tinnitus	3.7	3.8
Hemic and Lymphatic System		
Neutropenia	3.1	2.9
Metabolism and Nutrition		
Anorexia	10.1	9.5
Nervous System		
Headache	8.5	8.7
Insomnia	2.9	3.1
Respiratory System		
Hiccups	10.8	5.6

In addition, isolated cases of serious adverse experiences, regardless of causality, of bradycardia, disorientation, and perforating duodenal ulcer were reported in highly emetogenic CINV clinical studies.

Moderately Emetogenic Chemotherapy

During Cycle 1 of a moderately emetogenic chemotherapy study, 438 patients were treated with the aprepitant regimen and 385 of these patients continued into the Multiple-Cycle extension for up to 4 cycles of chemotherapy. In Cycle 1, clinical adverse experiences were reported in approximately 73% of patients treated with the aprepitant regimen compared with approximately 75% of patients treated with standard therapy.

The adverse experience profile in the moderately emetogenic chemotherapy study was generally comparable to the highly emetogenic chemotherapy studies. Table 5 shows the percent of patients with clinical adverse experiences reported at an incidence ≥3%.

Table 5
Percent of Patients Receiving Moderately Emetogenic Chemotherapy With Clinical Adverse Experiences (Incidence ≥3%) — Cycle 1

	Aprepitant Regimen (N = 438)	Standard Therapy (N = 428)
Blood and Lymphatic System Disorders		
Neutropenia	8.9	8.4
Metabolism and Nutrition Disorders		
Anorexia	4.3	5.8
Psychiatric Disorders		
Insomnia	4.1	5.6
Nervous System Disorders		
Dizziness	3.4	4.2
Headache	16.4	16.4
Vascular Disorders		
Hot Flush	3.0	1.4
Respiratory, Thoracic and Mediastinal Disorders		
Pharyngolaryngeal pain	3.0	2.3
Gastrointestinal Disorders		
Constipation	12.3	18.0
Diarrhea	5.5	6.3

Dyspepsia	8.4	4.9
Nausea	7.1	7.5
Stomatitis	5.3	4.4
Skin and Subcutaneous Tissue Disorders		
Alopecia	24.0	22.2
General Disorders and General Administration Site Conditions		
Asthenia	3.4	3.7
Fatigue	21.9	21.5
Mucosal inflammation	2.5	3.5

Isolated cases of serious adverse experiences, regardless of causality, of dehydration, enterocolitis, febrile neutropenia, hypertension, hypoesthesia, neutropenic sepsis, pneumonia, and sinus tachycardia were reported in the moderately emetogenic CINV clinical study.

Highly and Moderately Emetogenic Chemotherapy

The following additional clinical adverse experiences (incidence >0.5% and greater than standard therapy), regardless of causality, were reported in patients treated with aprepitant regimen:
Infections and infestations: candidiasis, herpes simplex, lower respiratory infection, pharyngitis, septic shock, upper respiratory infection, urinary tract infection.
Neoplasms benign, malignant and unspecified (including cysts and polyps): malignant neoplasm, non-small cell lung carcinoma.
Blood and lymphatic system disorders: anemia, febrile neutropenia, thrombocytopenia.
Metabolism and nutrition disorders: appetite decreased, diabetes mellitus, hypokalemia.
Psychiatric disorders: anxiety disorder, confusion, depression.
Nervous system: peripheral neuropathy, sensory neuropathy, taste disturbance, tremor.
Eye disorders: conjunctivitis.
Cardiac disorders: myocardial infarction, palpitations, tachycardia.
Vascular disorders: deep venous thrombosis, flushing, hypertension, hypotension.
Respiratory, thoracic and mediastinal disorders: cough, dyspnea, nasal secretion, pneumonitis, pulmonary embolism, respiratory insufficiency, vocal disturbance.
Gastrointestinal disorders: acid reflux, deglutition disorder, dry mouth, dysgeusia, dysphagia, eructation, flatulence, obstipation, salivation increased.
Skin and subcutaneous tissue disorders: acne, diaphoresis, rash.
Musculoskeletal and connective tissue disorders: arthralgia, back pain, muscular weakness, musculoskeletal pain, myalgia.
Renal and urinary disorders: dysuria, renal insufficiency.
Reproductive system and breast disorders: pelvic pain.
General disorders and administrative site conditions: edema, malaise, rigors.
Investigations: weight loss.

Laboratory Adverse Experiences

Table 6 shows the percent of patients with laboratory adverse experiences reported at an incidence ≥3% in patients receiving highly emetogenic chemotherapy.

Table 6

Percent of Patients Receiving Highly Emetogenic Chemotherapy With Laboratory Adverse Experiences (Incidence ≥3%) - Cycle 1

	Aprepitant Regimen (N = 544)	Standard Therapy (N = 550)
ALT Increased	6.0	4.3
AST Increased	3.0	1.3
Blood Urea Nitrogen Increased	4.7	3.5
Serum Creatinine Increased	3.7	4.3
Proteinuria	6.8	5.3

The following additional laboratory adverse experiences (incidence >0.5% and greater than standard therapy), regardless of causality, were reported in patients treated with aprepitant regimen: alkaline phosphatase increased, hyperglycemia, hyponatremia, leukocytes increased, erythrocyturia, leukocyturia.

The adverse experiences of increased AST and ALT were generally mild and transient.

The following laboratory adverse experiences were reported at an incidence ≥3% during Cycle 1 of the moderately emetogenic chemotherapy study in patients treated with the aprepitant regimen or standard therapy, respectively: decreased hemoglobin (2.3%, 4.7%) and decreased white blood cell count (9.3%, 9.0%).

The adverse experience profiles in the Multiple-Cycle extensions for up to 6 cycles of chemotherapy were generally similar to that observed in Cycle 1.

Stevens-Johnson syndrome was reported as a serious adverse experience in a patient receiving aprepitant with cancer chemotherapy in another CINV study.

Other Studies with Postoperative Nausea and Vomiting

In well-controlled clinical studies in patients receiving general anesthesia, 564 patients were administered 40 mg aprepitant orally and 538 patients were administered 4 mg ondansetron I.V. EMEND was generally well tolerated. Most adverse experiences reported in these clinical studies were described as mild to moderate in intensity. Clinical adverse experiences were reported in approximately 60% of patients treated with 40 mg aprepitant compared with approximately 64% of patients treated with 4 mg ondansetron I.V.

Additional adverse experiences were observed in patients receiving general anesthesia. In the patients treated with aprepitant (40 mg) for postoperative nausea and vomiting, the following additional adverse experiences were reported, regardless of causality, at an incidence ≥3%: anemia, bradycardia, flatulence, hypotension, pruritus, pyrexia.

The following adverse experiences were reported, regardless of causality, in patients treated with aprepitant for postoperative nausea and vomiting at an incidence of >0.5% and greater than with ondansetron: abdominal pain, abdominal pain upper, blood pressure decreased, dizziness, dyspepsia, hematoma, hypoesthesia, hypothermia, hypovolemia, hypoxia, operative hemorrhage, pain, postoperative infection, respiratory depression, syncope, urticaria, wound dehiscence.

Other adverse experiences (incidence ≤0.5%) reported, regardless of causality, in patients treated with aprepitant 40 mg for postoperative nausea and vomiting included: bowel sounds abnormal, dysarthria, miosis, sensory disturbance, stomach discomfort, visual acuity reduced, wheezing.

Laboratory Adverse Experiences with Postoperative Nausea and Vomiting

One laboratory adverse experience, hemoglobin decreased (40 mg aprepitant), was reported, regardless of causality, at an incidence ≥3% in a patient receiving general anesthesia.

The following additional laboratory adverse experiences (incidence >0.5% and greater than ondansetron), regardless of causality, were reported in patients treated with aprepitant 40 mg: blood albumin decreased, blood bilirubin increased, blood glucose increased, blood potassium decreased, glucose urine present.

The adverse experience of ALT increased occurred with similar incidence in patients treated with aprepitant as in patients treated with ondansetron.

Other Studies

In addition, two serious adverse experiences were reported in postoperative nausea and vomiting (PONV) clinical studies in patients taking a higher dose of aprepitant: one case of constipation, and one case of sub-ileus.

Angioedema and urticaria were reported as serious adverse experiences in a patient receiving aprepitant in a non-CINV/non-PONV study.

OVERDOSAGE

No specific information is available on the treatment of overdosage. Single doses up to 200 mg of fosaprepitant I.V. and 600 mg of oral aprepitant were generally well tolerated in healthy subjects.

Three out of 33 subjects receiving 200 mg of fosaprepitant experienced mild injection site thrombosis. Aprepitant was generally well tolerated when administered as 375 mg once daily for up to 42 days to patients in non-CINV studies. In 33 cancer patients, administration of a single 375-mg dose of aprepitant on Day 1 and 250 mg once daily on Days 2 to 5 was generally well tolerated.

Drowsiness and headache were reported in one patient who ingested 1440 mg of aprepitant.

In the event of overdose, oral aprepitant should be discontinued and general supportive treatment and monitoring should be provided. Because of the antiemetic activity of aprepitant, drug-induced emesis may not be effective.

Aprepitant cannot be removed by hemodialysis.

DOSAGE AND ADMINISTRATION

EMEND for Injection is a sterile, lyophilized prodrug of aprepitant containing polysorbate 80 (PS80), to be administered intravenously as an infusion. Aprepitant is available as capsules (EMEND[2]) for oral administration.

EMEND for Injection (115 mg) may be substituted for EMEND (125 mg) 30 minutes prior to chemotherapy, on Day 1 only of the CINV regimen as an infusion administered over 15 minutes.

EMEND for Injection should not be mixed or reconstituted with solutions for which physical and chemical compatibility have not been established. EMEND for Injection is incompatible with any solutions containing divalent cations (e.g., Ca^{2+}, Mg^{2+}), including Lactated Ringer's Solution and Hartmann's Solution.

The 3-day CINV regimen includes EMEND for Injection (115 mg) or EMEND (125 mg orally) on Day 1; EMEND (80 mg orally) on Days 2 and 3; in addition to a corticosteroid and a 5-HT_3 antagonist as specified in the tables below.

In clinical studies with EMEND, the following regimen was used for the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy:

	Day 1	Day 2	Day 3	Day 4
EMEND*	125 mg orally	80 mg orally	80 mg orally	none
Dexamethasone**	12 mg orally	8 mg orally	8 mg orally	8 mg orally
Ondansetron†	32 mg I.V.	none	none	none

*EMEND was administered orally 1 hour prior to chemotherapy treatment on Day 1 and in the morning on Days 2 and 3.
**Dexamethasone was administered 30 minutes prior to chemotherapy treatment on Day 1 and in the morning on Days 2 through 4. The dose of dexamethasone was chosen to account for drug interactions.
†Ondansetron was administered 30 minutes prior to chemotherapy treatment on Day 1.

In a clinical study with EMEND, the following regimen was used for the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy:

	Day 1	Day 2	Day 3
EMEND*	125 mg orally	80 mg orally	80 mg orally
Dexamethasone**	12 mg orally	none	none
Ondansetron†	2 x 8 mg orally	none	none

*EMEND was administered orally 1 hour prior to chemotherapy treatment on Day 1 and in the morning on Days 2 and 3.
**Dexamethasone was administered 30 minutes prior to chemotherapy treatment on Day 1. The dose of dexamethasone was chosen to account for drug interactions.
†Ondansetron 8-mg capsule was administered 30 to 60 minutes prior to chemotherapy treatment and one 8-mg capsule was administered 8 hours after the first dose on Day 1.

Preparation of EMEND for Injection

1. Aseptically inject 5 mL 0.9% Sodium Chloride for Injection (saline) into the vial. Assure that saline is added to the vial along the vial wall in order to prevent foaming. Swirl the vial gently. Avoid shaking and jetting saline into the vial.
2. Aseptically prepare an infusion bag filled with 110 mL of saline.
3. Aseptically withdraw the entire volume from the vial and transfer it into the infusion bag containing 110 mL of saline to yield a total volume of 115 mL and a final concentration of 1 mg/1 mL.
4. Gently invert the bag 2-3 times.

The reconstituted final drug solution is stable for 24 hours at ambient room temperature (at or below 25°C).

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration whenever solution and container permit.

Caution: EMEND for Injection should not be mixed or reconstituted with solutions for which physical and chemical compatibility have not been established. EMEND for Injection is incompatible with any solutions containing divalent cations (e.g., Ca^{2+}, Mg^{2+}), including Lactated Ringer's Solution and Hartmann's Solution.

[2] Registered trademark of MERCK & CO., Inc.

General Information

EMEND for Injection has not been studied for the treatment of established nausea and vomiting.

Chronic continuous administration is not recommended (see PRECAUTIONS).

See PRECAUTIONS, *Drug Interactions* for additional information on dose adjustment for corticosteroids when coadministered with EMEND for Injection.

Refer to the full prescribing information for coadministered antiemetic agents.

EMEND for Injection may be administered with or without food.

No dosage adjustment is necessary for the elderly.

No dosage adjustment is necessary for patients with renal insufficiency or for patients with end stage renal disease undergoing hemodialysis.

No dosage adjustment is necessary for patients with mild to moderate hepatic insufficiency (Child-Pugh score 5 to 9). There are no clinical data in patients with severe hepatic insufficiency (Child-Pugh score >9).

HOW SUPPLIED

No. 3884 — One 115 mg single dose per 10 mL glass vial: White to off-white lyophilized solid. Supplied as follows:

NDC 0006-3884-32 1 vial per carton.

Storage

Vials: Store at 2-8°C (36-46°F).

Sterile lyophilized powder for intravenous use only after reconstitution and dilution

Rx only

Manufactured for:

MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Manufactured by:

DSM Pharmaceuticals, Inc., 5900 Martin Luther King Jr. Highway, Greenville, NC 27834

U.S. Patent Nos.: 5,512,570; 5,691,336

Issued 2008
Printed in USA

Patient Information
EMEND®
(fosaprepitant dimeglumine)
for Injection

You should read this information before you start taking EMEND[1] (fosaprepitant dimeglumine) for Injection. Also, read the leaflet each time you refill your prescription, in case any information has changed. This leaflet provides only a summary of certain information about EMEND for Injection. Your doctor or pharmacist can give you an additional leaflet that is written for health professionals that contains more complete information. This leaflet does not take the place of careful discussions with your doctor. You and your doctor should discuss EMEND for Injection when you start taking your medicine.

What is EMEND for Injection?

EMEND for Injection is an antiemetic medicine for use in adult patients, to be given intravenously by your doctor. An antiemetic is a medicine used to prevent and control nausea and vomiting. EMEND for Injection is always used WITH OTHER MEDICINES to prevent and control nausea and vomiting caused by your chemotherapy treatment. EMEND for Injection is not used to treat nausea and vomiting that you already have.

Who should not take EMEND for Injection?

Do not take EMEND for Injection if you:

- are taking any of the following medicines[2]:
  - ORAP® (pimozide)
  - SELDANE® (terfenadine)
  - HISMANAL® (astemizole)
  - PROPULSID® (cisapride)

Taking EMEND for Injection with these medicines could cause serious or life-threatening problems.

- are allergic to fosaprepitant or any of the ingredients in EMEND for Injection. The active ingredient is fosaprepitant. See the end of this leaflet for a list of all the ingredients in EMEND for Injection.

What should I tell my doctor before and during treatment with EMEND for Injection?

Tell your doctor:

- if you are pregnant or plan to become pregnant. It is not known if EMEND for Injection can harm your unborn baby.
- if you are breast-feeding. It is not known if EMEND for Injection passes into your milk and if it can harm your baby.
- if you have liver problems.
- about all your medical problems.
- about all the medicines that you are taking or plan to take, prescription and nonprescription medicines, vitamins, and herbal supplements. EMEND for Injection may cause **serious life-threatening reactions** if used with certain medicines (see the section **Who should not take EMEND**

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[1] Trademark of MERCK & CO., Inc.

[2] The brands listed are the registered trademarks of their respective owners and are not trademarks of Merck & Co., Inc.

for Injection?). Some medicines can affect EMEND for Injection. EMEND for Injection may also affect some medicines, including chemotherapy, causing them to work differently in your body.

Your doctor may check to make sure your other medicines are working, while you are taking EMEND for Injection. Patients who take COUMADIN® (warfarin) may need to have blood tests after each 3-day treatment to check their blood clotting.

Women who use birth control medicines during treatment with EMEND for Injection and for up to 1 month after using EMEND for Injection should also use a back-up method of contraception to avoid pregnancy.

How should I take EMEND for Injection?

- EMEND for Injection is given intravenously on Day 1 only of a 3-day regimen.

The recommended dose of EMEND for Injection is:
- 115 mg given intravenously 30 minutes before you start your chemotherapy treatment;
  AND
- One 80-mg capsule of EMEND[3] (aprepitant) each morning for the 2 days following your chemotherapy treatment.
- EMEND for Injection may be administered with or without food.
- Tell your doctor if you already have nausea and vomiting before you are given EMEND for Injection.

What are the possible side effects of EMEND for Injection?

The most common side effects of EMEND for Injection are:

- tiredness
- nausea
- hiccups
- constipation
- diarrhea
- loss of appetite
- headache
- hair loss
- injection site pain
- hardening of site of injection

These are not all of the possible side effects of EMEND for Injection. For further information ask your doctor or pharmacist. Talk to your doctor about any side effect that bothers you.

General information about the use of EMEND for Injection

This leaflet summarizes the most important information about EMEND for Injection. If you would like to know more information, talk with your doctor. You can ask your doctor or pharmacist for information about EMEND for Injection that is written for health professionals.

What are the ingredients in EMEND for Injection?

Active ingredient: fosaprepitant

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[3] Registered trademark of MERCK & CO., Inc.

Inactive ingredients: edetate disodium, polysorbate 80, lactose anhydrous, sodium hydroxide and/or hydrochloric acid (for pH adjustment).
U.S. Patent Nos.: 5,512,570; 5,691,336

Issued January 2008

Manufactured for:

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EXHIBIT E

U.S. Patent No. 5,691,336

US005691336A

United States Patent [19]

Dorn et al.

[11] Patent Number: 5,691,336

[45] Date of Patent: Nov. 25, 1997

[54] MORPHOLINE COMPOUNDS ARE PRODRUGS USEFUL AS TACHYKININ RECEPTOR ANTAGONISTS

[75] Inventors: **Conrad P. Dorn**, Plainfield; **Jeffrey J. Hale**, Westfield; **Malcolm Maccoss**, Freehold; **Sander G. Mills**, Woodbridge, all of N.J.

[73] Assignee: **Merck & Co., Inc.**, Rahway, N.J.

[21] Appl. No.: **525,870**

[22] Filed: **Sep. 8, 1995**

Related U.S. Application Data

[63] Continuation-in-part of PCT/US95/02551 Feb. 28, 1995, continuation-in-part of Ser. No. 206,771, Mar. 4, 1994, abandoned.

[51] **Int. Cl.**[6] **C07D 265/32**; C07D 279/12; C07D 413/04; C07D 413/06; C07D 413/14

[52] **U.S. Cl.** **514/236.2**; 514/233.5; 514/235.2; 514/235.5; 514/235.8; 544/132; 544/134; 544/139; 544/141; 544/143

[58] **Field of Search** 544/132, 134, 544/139, 141, 143; 514/235.2, 235.5, 235.8, 233.5, 236.2

[56] **References Cited**

U.S. PATENT DOCUMENTS

2,943,022	6/1960	Siemer et al.	167/65
3,005,818	10/1961	Siemer et al.	260/247.2
3,458,509	7/1969	Levine et al.	260/243
3,506,673	4/1970	Warawa et al.	260/294.7
3,541,090	11/1970	Herlinger et al.	260/243
4,010,266	3/1977	McLoughlin et al.	424/248.4
4,360,519	11/1982	White et al.	424/248.55
4,476,311	10/1984	Shetty et al.	424/243
4,705,553	11/1987	Buschmenn et al.	71/76
4,782,054	11/1988	Regnier et al.	514/235.2
4,943,578	7/1990	Naylor et al.	514/252
5,064,838	11/1991	Carr et al.	514/317
5,095,021	3/1992	Zipplies et al.	167/65

FOREIGN PATENT DOCUMENTS

0 360 390	3/1990	European Pat. Off.	514/235.2
0 436 334	7/1991	European Pat. Off.	544/132
0 499 313	8/1992	European Pat. Off.	514/235.2
0 528 495	2/1993	European Pat. Off.	544/132
0 533 280 A1	3/1993	European Pat. Off.	544/132
2534915	4/1984	France	544/132
WO 90/05525	5/1990	WIPO	514/235.2
WO 90/05729	5/1990	WIPO	514/235.2
WO 91/18899	12/1991	WIPO	514/235.2
WO 92/01679	2/1992	WIPO	514/252
WO 92/06079	4/1992	WIPO	514/235.2
WO 92/12128	7/1992	WIPO	514/317
WO 92/12151	7/1992	WIPO	514/317
WO 92/12152	7/1992	WIPO	514/252
WO 94/00440	1/1994	WIPO	544/132
WO 95/16679	6/1995	WIPO	544/132

OTHER PUBLICATIONS

Advenier, et al., "Neurokinin A (NK2) Receptor Revisited With SR48968 . . . ", *Biochem. and Biophys., Res. Comm.*, 184(3), pp. 1418–1424 (1992).

Edmonds–Alt, et al., "A Potent and Selective Non–Peptide Antagonist of the Neurokinin A (NK2) Receptor", *Life Sci.*, 50, pp. PL101–PL106 (1992).

Frossard, et al. "Tachykinin Receptors and the Airways", *Life Sci.*, 49, pp. 1491–1953, (1991).

Guthrie, et al., "The Use of Periodate–Oxidized Glycosides in the Robinson–Schopf . . . ", *J. Chem. Society*, vol. C(1), pp. 62–66 (1967).

Howson, et al., "An SAR Study for the Non–Peptide Substance P Receptor . . . ", *Biorg. & Med. Chem. Lett.*, vol. 2(6), pp. 559–564 (1992).

G. Rucker, et al., *Arch. Pharm.*, (Weinheim, Ger.) 315(10), 839–846 (1982), "Stabilitasuntersuchungen and Phenylethylaminsubstituierten Pyrazolonein".

Chem. Abstracts, 73 (3) p. 361, No. 14777c (Jul. 20, 1970), "Diastereoisomeric Configuration of Morpholine Derivatives".

I.V. Bozhko, et al., *Kinet. Katal.*, 31 (3), 737–738 (1990) (Russ.).

Lowe, et al., "The Discovery of (2S, 3S)–cis–2(Diphenylmethyl)–N–(2–methoxyphenyl)methyl . . . ", *J. Med. Chem.*, vol. 35, pp. 2591–2600 (1992).

McCormick, "Properties of Periodate–Oxidised Polysaccharides", *J. Chem. Society*, vol. C(23), pp. 2121–2127 (1966).

Montgomery, et al., "2–Fluoropurine Ribonucleosides", *J. of Med. Chem.*, vol. 13(3), pp. 421–427 (1970).

Payan, et al., "Substance P. Recognition by a Subset of Human T Lymphocytes", *J. Clin. Invest.*, 74, 1532–1539 (1984).

Peyronel, et al., "Synthesis of RP–67,580, a New Potent Nonpeptide Subtance P Antagonist", *Biorg. and Med. Chem. Lett.*, vol. 2(6), pp. 559–564 (1992).

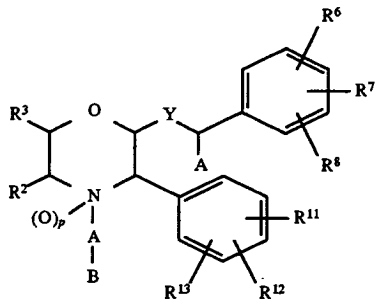
Siemer, et al., "Analgesic 1–phenyl–2, 3–dimethyl–4–morpholinomethyl–3–pyrazolin–5–ones . . . " *Chem. Abstracts*, 56, No. 6, No. 5977e (1962).

(List continued on next page.)

Primary Examiner—Floyd D. Higel
Attorney, Agent, or Firm—J. Eric Thies; David L. Rose

[57] **ABSTRACT**

Substituted heterocycles of the general structural formula:



are tachykinin receptor antagonists useful in the treatment of inflammatory diseases, pain or migraine, asthma, and emesis.

25 Claims, No Drawings

OTHER PUBLICATIONS

Chem. Abstracts, 113 (20) p. 123, No. 174441m (Nov. 12, 1990), "Amine Hydrochlorides–Catalysts for Hydrochlorination".

Sinkula, et al., "Rationale for Design of Biologically Reversible Drug Derivatives: Prodrugs", *J. Pharm. Sciences,* 64 (2), pp. 181–210 (1975).

Svensson, "Prodrugs: metabolism–based drug design", *Pharmaceutisch Weekblad,* 122, pp. 245–250, (1987).

Balant, et al., "Prodrugs for the improvement of drug absorption via different routes of administration.", *Eur. J. Drug Metab. Pharmaco.,* 15(2), pp. 143–153, (1990).

Bodar, et al., "Novel Approaches in Prodrug Design", *Drugs Future,* VI(3), pp. 165–182 (1981).

Bundgaard, "The double prodrug concept and its applications", *Adv. Drug Delivey Rev.,* 3 pp. 39–65, (1989).

MORPHOLINE COMPOUNDS ARE PRODRUGS USEFUL AS TACHYKININ RECEPTOR ANTAGONISTS

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of PCT application U.S. Ser. No. 95/02551, filed Feb. 28, 1995, and a continuation-in-part of application Ser. No. 08/206,771 filed Mar. 4, 1994, now abandoned.

BACKGROUND OF THE INVENTION

Analgesia has historically been achieved in the central nervous system by opiates and analogs which are addictive, and peripherally by cyclooxygenase inhibitors that have gastric side effects. Substance P antagonists may induce analgesia both centrally and peripherally. In addition, substance P antagonists are inhibitory of neurogenic inflammation.

The neuropeptide receptors for substance P (neurokinin-1; NK-1) are widely distributed throughout the mammalian nervous system (especially brain and spinal ganglia), the circulatory system and peripheral tissues (especially the duodenum and jejunum) and are involved in regulating a number of diverse biological processes. This includes sensory perception of olfaction, vision, audition and pain, movement control, gastric motility, vasodilation, salivation, and micturition (B. Pernow, *Pharmacol. Rev.*, 1983, 35, 85–141). The NK1 and NK2 receptor subtypes are implicated in synaptic transmission (Laneuville et al., *Life Sci.*, 42: 1295–1305 (1988)).

The receptor for substance P is a member of the superfamily of G protein-coupled receptors. This superfamily is an extremely diverse group of receptors in terms of activating ligands and biological functions. In addition to the tachykinin receptors, this receptor superfamily includes the opsins, the adrenergic receptors, the muscarinic receptors, the dopamine receptors, the serotonin receptors, a thyroid-stimulating hormone receptor, a luteinizing hormone-choriogonadotropic hormone receptor, the product of the oncogene ras, the yeast mating factor receptors, a Dictyostelium cAMP receptor, and receptors for other hormones and neurotransmitters (see A. D. Hershey, et al., *J. Biol. Chem.*, 1991, 226, 4366–4373).

Substance P (also called "SP" herein) is a naturally occurring undecapeptide belonging to the tachykinin family of peptides, the latter being so-named because of their prompt contractile action on extravascular smooth muscle tissue. The tachykinins are distinguished by a conserved carboxyl-terminal sequence Phe-X-Gly-Leu-Met-NH_2. In addition to SP the known mammalian tachykinins include neurokinin A and neurokinin B. The current nomenclature designates the receptors for SP, neurokinin A, and neurokinin B as NK-1, NK-2, and NK-3, respectively.

More specifically, substance P is a pharmacologically-active neuropeptide that is produced in mammals and possesses a characteristic amino acid sequence (Chang et al., *Nature New Biol.* 232, 86 (1971); D. F. Veber et al., U.S. Pat. No. 4,680,283.

Substance P is a pharmacologically-active neuropeptide that is produced in mammals and acts as a vasodilator, a depressant, stimulates salivation and produces increased capillary permeability. It is also capable of producing both analgesia and hyperalgesia in animals, depending on dose and pain responsiveness of the animal (see R. C. A. Frederickson et al., *Science*, 199, 1359 (1978); P. Oehme et al., *Science*, 208, 305 (1980)) and plays a role in sensory transmission and pain perception (T. M. Jessell, *Advan. Biochem. Psychopharmacol.* 28, 189 (1981)). For example, substance P is believed to be involved in the neurotransmission of pain sensations [Otsuka et al, "Role of Substance P as a Sensory Transmitter in Spinal Cord and Sympathetic Ganglia" in 1982 Substance P in the Nervous System, Ciba Foundation Symposium 91, 13–34 (published by Pitman) and Otsuka and Yanagisawa, "Does Substance P Act as a Pain Transmitter?" *TIPS*, 8 506–510 (December 1987)], specifically in the transmission of pain in migraine (see B. E. B. Sandberg et al., *Journal of Medicinal Chemistry*, 25, 1009 (1982); M. A. Moskowitz, *Trends Phamacol. Sci.*, 13, 307–311 (1992)), and in arthritis (Levine, et al. *Science*, 226 547–549 (1984); M. Lotz, et al., *Science*, 235, 893–895 (1987)). Tachykinins have also been implicated in gastrointestinal (GI) disorders and diseases of the GI tract, such as inflammatory bowel disease [see Mantyh et al., *Neuroscience*, 25 (3), 817–37 (1988) and D. Regoli in "Trends in Cluster Headache" Ed. F. Sicuteri et al., Elsevier Scientific Publishers, Amsterdam, pp. 85–95 (1987)], and emesis [*Trends Pharmacol. Sci.*, 9, 334–341 (1988), F. D. Tatersall, et al., *Eur. J. Pharmacol.*, 250, R5–R6 (1993)].

It is also hypothesized that there is a neurogenic mechanism for arthritis in which substance P may play a role [Kidd et al., "A Neurogenic Mechanism for Symmetric Arthritis" in *The Lancet*, 11 Nov. 1989 and Gronblad et al., "Neuropeptides in Synovium of Patients with Rheumatoid Arthritis and Osteoarthritis" in *J. Rheumatol.* 15(12) 1807–10 (1988)]. Therefore, substance P is believed to be involved in the inflammatory response in diseases such as rheumatoid arthritis and osteoarthritis [O'Byrne et al., *Arthritis and Rheumatism*, 33 1023–8 (1990)].

Evidence for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, Alzheimer's disease, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory diseases such as rheumatoid arthritis, asthma/bronchial hyperreactivity and other respiratory diseases including allergic rhinitis, inflammatory diseases of the gut including ulcerative colitis and Chrohn's disease, ocular injury and ocular inflammatory diseases, proliferative vitreoretinopathy, irritable bowel syndrome and disorders of bladder function including cystitis and bladder detruser hyperreflexia is reviewed in "Tachykinin Receptors and Tachykinin Receptor Antagonists," C. A. Maggi, R. Patacchini, P. Rovero and A. Giachetti, *J. Auton. Pharmacol*, 13, 23–93 (1993); see also R. M. Snider, et al., *Chem. Ind.*, 11, 792–794 (1991). Neurokinin-1 receptor antagonists alone or in combination with bradykinin receptor antagonists may also be useful in the prevention and treatment of inflammatory conditions in the lower urinary tract, especially cystitis [Giuliani, et al., *J. Urology*, 150, 1014–1017 (1993)]. Other disease areas where tachykinin antagonists are believed to be useful are allergic conditions [Hamelet et al., *Can. J. Pharmacol. Physiol.*, 66, 1361–7 (1988)], immunoregulation [Lotz, et al., *Science*, 241 1218–21 (1988), Kimball, et al., *J. Immunol.*, 141 (10) 3564–9 (1988); A. Perianin, et al., *Biochem. Biophys. Res Commun.* 161, 520 (1989)], post-operative pain and nausea [C. Bountra, et al., *Eur. J. Pharmacol., 249,* R3–R4 (1993), F. D. Tattersall, et al., *Neuropharmacology*, 33, 259–260 (1994)], vasodilation, bronchospasm, reflex or neuronal control of the viscera [Mantyh et al., *PNAS*, 85, 3235–9 (1988)] and, possibly by arresting or slowing β-amyloid-mediated neurodegenerative

changes [Yankner et al., *Science*, 250, 279–82 (1990)] in senile dementia of the Alzheimer type, Alzheimer's disease and Downs Syndrome. Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis [J. Luber-Narod, et. al., poster C.I.N.P. XVIIIth Congress, 28th Jun.–2nd Jul., 1992], and in disorders of bladder function such as bladder detrusor hyperreflexia [*Lancet*, 16th May 1992, 1239]. Antagonists selective for the neurokinin-1 (NK-1) and/or the neurokinin-2 (NK-2) receptor may be useful in the treatment of asthmatic disease (Frossard et al., *Life Sci.*, 49, 1941–1953 (1991); Advenier, et al., *Biochem. Biophys. Res. Comm.*, 184(3), 1418–1424 (1992); P. Barnes, et al., *Trends Pharmacol. Sci.*, 11, 185–189 (1993)). Tachykinin antagonists may also be useful in the treatment of small cell carcinomas, in particular small cell lung cancer (SCLC) [Langdon et al., *Cancer Research*, 52, 4554–7 (1992)].

It has furthermore been suggested that tachykinin receptor antagonists have utility in the following disorders: depression, dysthymic disorders, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina and Reynauld's disease, fibrosing and collagen diseases such as scleroderma and eosinophillic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, neuropathy, neuralgia, disorder related to immune enhancement or suppression such as systemic lupus erythmatosus (EPO Publication No. 0,436,334), ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like, and cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis (EPO Publication No. 0,394,989).

Substance P antagonists may be useful in mediating neurogenic mucus secretion in mammalian airways and hence provide treatment and symptomatic relief in diseases characterized by mucus secretion, in particular, cystic fibrosis [S. Ramnarine, et al., abstract presented at 1993 ALA/ATS Int'l Conference, 16–19 May, 1993, published in *Am. Rev. of Respiratory Dis., May* 1993].

In the recent past, some attempts have been made to provide peptide-like substances that are antagonists for the receptors of substance P and other tachykinin peptides in order to more effectively treat the various disorders and diseases mentioned above. For example Lowe, *Drugs of the Future*, 17 (12) 1115–1121 (1992) and EPO Publication Nos. 0,347,802, 0,401,177 and 0,412,452 disclose various peptides as neurokinin A antagonists. Also, PCT Patent Publication WO 93/14113 discloses certain peptides as tachykinin antagonists. In addition, EPO Publication No. 0,336,230 discloses heptapeptides which are substance P antagonists useful in the treatment of asthma. Merck U.S. Pat. No. 4,680,283 also discloses peptidal analogs of substance P. Certain inhibitors of tachykinins have been described in U.S. Pat. No. 4,501,733, by replacing residues in substance P sequence by Trp residues. A further class of tachykinin receptor antagonists, comprising a monomeric or dimeric hexa- or heptapeptide unit in linear or cyclic form, is described in GB-A-2216529.

The peptide-like nature of such substances make them too labile from a metabolic point of view to serve as practical therapeutic agents in the treatment of disease. The non-peptidic antagonists of the present invention, on the other hand, do not possess this drawback, as they are expected to be more stable from a metabolic point of view than the previously-discussed agents.

It is known in the an that baclofen (β-(aminoethyl)-4-chlorobenzenepropanoic acid) in the central nervous system effectively blocks the excitatory activity of substance P, and the excitatory responses to other compounds such as acetylcholine and glutamate are inhibited as well. Pfizer WIPO patent applications (PCT publication Nos. WO 90/05525, WO 90/05729, WO 91/18899, WO 92/12151 and WO 92/12152) and publications (*Science*, 251, 435–437 (1991); *Science*, 251, 437–439 (1991); *J. Med. Chem.*, 35, 2591–2600 (1992)) disclose 2-arylmethyl-3-substituted amino-quinuclidine derivatives which are disclosed as being useful as substance P antagonists for treating gastrointestinal disorders, central nervous system disorders, inflammatory diseases and pain or migraine. A Glaxo European patent application (EPO Publication No. 0,360,390) discloses various spirolactam-substituted amino acids and peptides which are antagonists or agonists of substance P. A Pfizer WIPO patent application (PCT Publication No. WO 92/06079) discloses fused-ring analogs of nitrogen-containing nonaromatic heterocycles as useful for the treatment of diseases mediated by an excess of substance P. A Pfizer WIPO patent application (PCT Publication No. WO 92/15585 discloses 1-azabicyclo[3.2.2]nonan-3-amine derivatives as substance P antagonists. A Pfizer WIPO patent application (PCT Publication No. WO 93/10073) discloses ethylenediamine derivatives as substance P antagonists. PCT Publication No. WO 93/01169 discloses certain aromatic compounds as tachykinin receptor antagonists. A Sanofi publication (*Life Sci.*, 50, PL101–PL106 (1992)) discloses a 4-phenyl piperidine derivative as an antagonist of the neurokinin A (NK2) receptor.

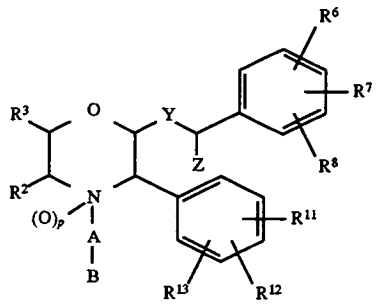
Howson et al. (*Biorg. & Med. Chem. Lett.*, 2 (6), 559–564 (1992)) disclose certain 3-amino and 3-oxy quinuclidine compounds and their binding to substance P receptors. EPO Publication 0,499,313 discloses certain 3-oxy and 3-thio azabicyclic compounds as tachykinin antagonists. U.S. Pat. No. 3,506,673 discloses certain 3-hydroxy quinuclidine compounds as central nervous system stimulants. A Pfizer EPO Patent application (EPO Publication 0,436,334) discloses certain 3-aminopiperidine compounds as substance P antagonists. U.S. Pat. No. 5,064,838 discloses certain 1,4-disubstituted piperidinyl compounds as analgesics. PCT Publication No. WO 92/12128 discloses certain piperidine and pyrrolidine compounds as analgesics. Peyronel, et al. (*Biorg & Med. Chem. Lett.*, 2 (1), 37–40 (1992)) disclose a fused ring pyrrolidine compound as a substance P antagonist. EPO Publication No. 0,360,390 discloses certain spirolactam derivatives as substance P antagonists. U.S. Pat. No. 4,804,661 discloses certain piperazine compounds as analgesics. U.S. Pat. No. 4,943,578 discloses certain piperazine compounds useful in the treatment of pain. PCT Publication No. WO 92/01679 discloses certain 1,4-disubstituted piperazines useful in the treatment of mental disorders in which a dopaminergic deficit is implicated. PCT Publication No. WO 94/00440, EPO Publication No. 0,577,394 and PCT Publication No. WO 95/16679 disclose certain morpholine and thiomorpholine substance P antagonists, some of which are the parent compounds to the instant prodrugs.

Prodrugs are entities structurally related to a biologically active substance (the "parent drug") which, after administration, release the parent drug in vivo as the result of some metabolic process, such as enzymatic or chemical hydrolysis of a carboxylic, phosphoric or sulfate ester or reduction or oxidation of a susceptible functionality (see, for example, discussions by (1) A. A. Sinkula and S. H. Yalkowsky, *J. Pharm. Sci.* 64, 181 (1975); (2) L. A. Svensson, *Pharm Weekbl*, 122, 245–250 (1987); (3) L. P. Balant, E. Doelker and P. Buri *Eur. J. Drug Metab. and Pharmacokinetics*, 15, 143–153 (1990); (4) N. Bodor, *Drugs*

of the Future, 6, 165–182 (1981); (5) *Design of Biopharmaceutical Properties through Prodrugs and Analogs*, E. B. Roche, Ed., American Pharmaceutical Association Academy of Pharmaceutical Sciences, Washington, D.C., (1977); (6) H. Bundgaard *Advanced Drug Delivery Reviews*, 3, 39–65 (1989)). The advantage of a prodrug may lie in its physical properties, such as enhanced water solubility for parenteral administration compared to the parent drug, or it may enhance absorption from the digestive tract, or it may enhance drug stability for long-ten storage. In general, a prodrug possesses less biological activity than its parent drug.

SUMMARY OF THE INVENTION

This invention is concerned with novel compounds represented by structural formula I:



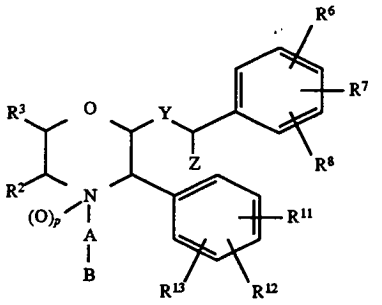
wherein R^2, R^3, R^6, R^7, R^8, R^{11}, R^{12}, R^{13}, A, B, p, Y and Z are hereinafter defined.

The invention is also concerned with pharmaceutical formulations comprising these novel compounds as active ingredients and the use of the novel compounds and their formulations in the treatment of certain disorders.

The compounds of this invention are tachykinin receptor antagonists and are useful in the treatment of inflammatory diseases, pain or migraine, asthma, and emesis.

DETAILED DESCRIPTION OF THE INVENTION

The novel compounds of this invention are represented by structural formula I:



or a pharmaceutically acceptable salt thereof, wherein:

R^2 and R^3 are independently selected from the group consisting of:

(1) hydrogen,

(2) C_{1-6} alkyl, unsubstituted or substituted with one or more of the substituents selected from:

(a) hydroxy,

(b) oxo,

(c) C_{1-6} alkoxy,

(d) phenyl-C_{1-3} alkoxy,

(e) phenyl,

(f) —CN,

(g) halo,

(h) $—NR^9R^{10}$, wherein R^9 and R^{10} are independently selected from:

(i) hydrogen,

(ii) C_{1-6} alkyl,

(iii) hydroxy-C_{1-6} alkyl, and

(iv) phenyl,

(i) $—NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,

(j) $—NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,

(k) $—CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,

(l) $—COR^9$, wherein R^9 is as defined above, and

(m) $—CO_2R^9$, wherein R^9 is as defined above;

(3) C_{2-6} alkenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:

(a) hydroxy,

(b) oxo,

(c) C_{1-6} alkoxy,

(d) phenyl-C_{1-3} alkoxy,

(e) phenyl,

(f) —CN,

(g) halo,

(h) $—CONR^9R^{10}$ wherein R^9 and R^{10} are as defined above,

(i) $—COR^9$ wherein R^9 is as defined above,

(j) $—CO_2R^9$, wherein R^9 is as defined above;

(4) C_{2-6} alkynyl;

(5) phenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:

(a) hydroxy,

(b) C_{1-6} alkoxy,

(c) C_{1-6} alkyl,

(d) C_{2-5} alkenyl,

(e) halo,

(f) —CN,

(g) $—NO_2$,

(h) $—CF_3$,

(i) $—(CH_2)_m—NR^9R^{10}$, wherein m, R^9 and R^{10} are as defined above,

(j) $—NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,

(k) $—NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,

(l) $—CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,

(m) $—CO_2NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,

(n) $—COR^9$, wherein R^9 is as defined above;

(o) $—CO_2R^9$, wherein R^9 is as defined above;

and, alternatively, the groups R^2 and R^3 are joined together to form a carbocyclic ring selected from the group consisting of:

(a) cyclopentyl,

(b) cyclohexyl,

(c) phenyl,

and wherein the carbocyclic ring is unsubstituted or substituted with one or more substituents selected from:

(i) C_{1-6}alkyl,

(ii) C_{1-6}alkoxy,

(iii) $—NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,

(iv) halo, and

(v) trifluoromethyl;

and, alternatively, the groups R^2 and R^3 are joined together to form a heterocyclic ring selected from the group consisting of:

(a) pyrrolidinyl,
(b) piperidinyl,
(c) pyrrolyl,
(d) pyridinyl,
(e) imidazolyl,
(f) furanyl,
(g) oxazolyl,
(h) thienyl, and
(i) thiazolyl,

and wherein the heterocyclic ring is unsubstituted or substituted with one or more substituent(s) selected from:

(i) C_{1-6}alkyl,
(ii) oxo,
(iii) C_{1-6}alkoxy,
(iv) $—NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(v) halo, and
(vi) trifluoromethyl;

R^6, R^7 and R^8 are independently selected from the group consisting of:

(1) hydrogen;
(2) C_{1-6} alkyl, unsubstituted or substituted with one or more of the substituents selected from:
(a) hydroxy,
(b) oxo,
(c) C_{1-6} alkoxy,
(d) phenyl-C_{1-3} alkoxy,
(e) phenyl,
(f) —CN,
(g) halo,
(h) $—NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(i) $—NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,
(j) $—NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,
(k) $—CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(l) $—COR^9$, wherein R^9 is as defined above, and
(m) $—CO_2R^9$, wherein R^9 is as defined above;
(3) C_{2-6} alkenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
(a) hydroxy,
(b) oxo,
(c) C_{1-6} alkoxy,
(d) phenyl-C_{1-3} alkoxy,
(e) phenyl,
(f) —CN,
(g) halo,
(h) $—CONR^9R^{10}$ wherein R^9 and R^{10} are as defined above,
(i) $—COR^9$ wherein R^9 is as defined above,
(j) $—CO_2R^9$, wherein R^9 is as defined above;
(4) C_{2-6} alkynyl;
(5) phenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
(a) hydroxy,
(b) C_{1-6} alkoxy,
(c) C_{1-6} alkyl,
(d) C_{2-5} alkenyl,
(e) halo,
(f) —CN,
(g) $—NO_2$,
(h) $—CF_3$,
(i) $—(CH_2)_m—NR^9R^{10}$, wherein m, R^9 and R^{10} are as defined above,
(j) $—NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,
(k) $—NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,
(l) $—CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(m) $—CO_2NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(n) $—COR^9$, wherein R^9 is as defined above;
(o) $—CO_2R^9$, wherein R^9 is as defined above;
(6) halo,
(7) —CN,
(8) $—CF_3$,
(9) $—NO_2$,
(10) $—SR^{14}$, wherein R^{14} is hydrogen or C_{1-5}alkyl,
(11) $—SOR^{14}$, wherein R^{14} is as defined above,
(12) $—SO_2R^{14}$, wherein R^{14} is as defined above,
(13) NR^9COR^{10}, wherein R^9 and R^{10} are as defined above,
(14) $CONR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,
(15) NR^9R^{10}, wherein R^9 and R^{10} are as defined above,
(16) $NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,
(17) hydroxy,
(18) C_{1-6}alkoxy,
(19) COR^9, wherein R^9 is as defined above,
(20) CO_2R^9, wherein R^9 is as defined above,
(21) 2-pyridyl,
(22) 3-pyridyl,
(23) 4-pyridyl,
(24) 5-tetrazolyl,
(25) 2-oxazolyl, and
(26) 2-thiazolyl;

R^{11}, R^{12} and R^{13} are independently selected from the definitions of R^6, R^7 and R^8, or —OX;

A is selected from the group consisting of:

(1) C_{1-6} alkyl, unsubstituted or substituted with one or more of the substituents selected from:
(a) hydroxy,
(b) oxo,
(c) C_{1-6} alkoxy,
(d) phenyl-C_{1-3} alkoxy,
(e) phenyl,
(f) —CN,
(g) halo, wherein halo is fluoro, chloro, bromo or iodo,
(h) $—NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(i) $—NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,
(j) $—NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,
(k) $—CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(l) $—COR^9$, wherein R^9 is as defined above, and
(m) $—CO_2R^9$, wherein R^9 is as defined above;
(2) C_{2-6} alkenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
(a) hydroxy,
(b) oxo,
(c) C_{1-6} alkoxy,
(d) phenyl-C_{1-3} alkoxy,
(e) phenyl,
(f) —CN,

(g) halo,

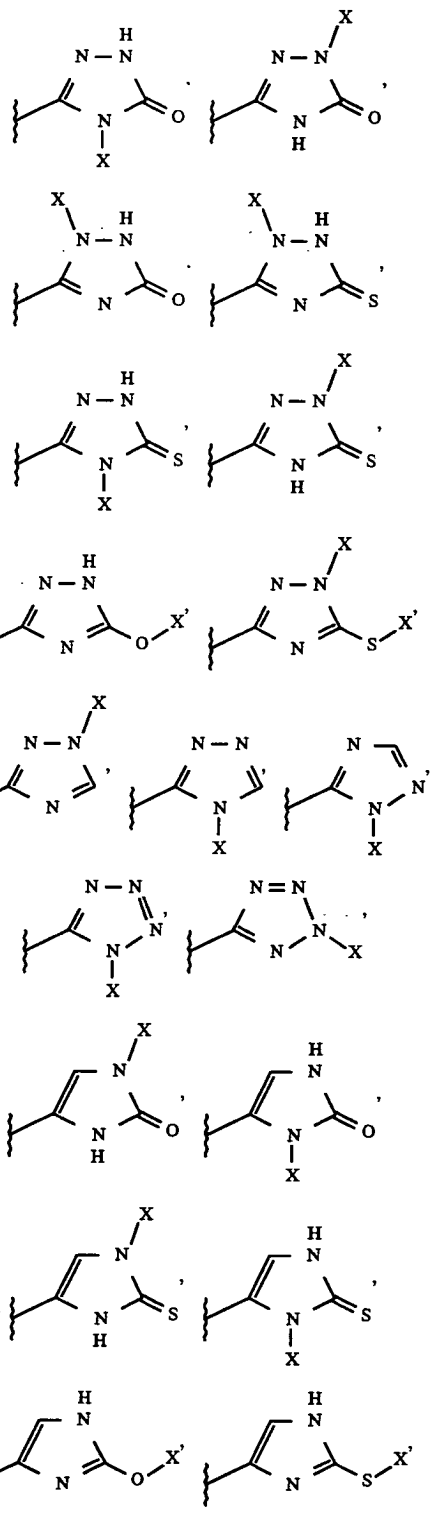
(h) —$CONR^9R^{10}$ wherein R^9 and R^{10} are as defined above,

(i) —COR^9 wherein R^9 is as defined above, and

(j) —CO_2R^9, wherein R^9 is as defined above; and

(3) C_{2-6} alkynyl;

B is a heterocycle, wherein the heterocycle is selected from the group consisting of:



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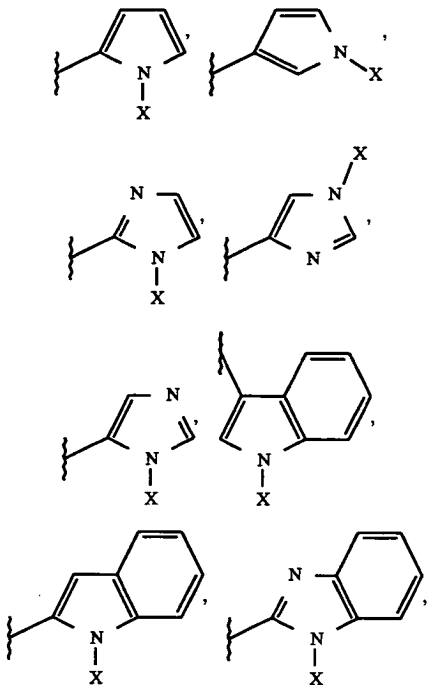


and wherein the heterocycle is substituted in addition to —X with one or more substituent(s) selected from:

(i) hydrogen

(ii) C_{1-6} alkyl, unsubstituted or substituted with halo, —CF_3, —OCH_3, or phenyl,

(iii) C_{1-6} alkoxy,

(iv) oxo,

(v) hydroxy,

(vi) thioxo,

(vii) —SR^9, wherein R^9 is as defined above,

(viii) halo,

(ix) cyano,

(x) phenyl,

(xi) trifluoromethyl,

(xii) —$(CH_2)_m$—NR^9R^{10}, wherein m is 0, 1 or 2, and R^9 and R^{10} are as defined above,

(xiii) —NR^9COR^{10}, wherein R^9 and R^{10} are as defined above,

(xiv) —$CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,

(xv) —CO_2R^9, wherein R^9 is as defined above, and

(xvi) —$(CH_2)_m$—OR^9, wherein m and R^9 are as defined above;

p is 0 or 1;

X is selected from:

(a) —$PO(OH)O^-{\cdot}M^+$, wherein M^+ is a pharmaceutically acceptable monovalent counterion,

(b) —$PO(O^-)_2{\cdot}2M^+$,

(c) —$PO(O^-)_2{\cdot}D^{2+}$, wherein D^{2+} is a pharmaceutically acceptable divalent counterion,

(d) —$CH(R^4)$—$PO(OH)O^-{\cdot}M^+$, wherein R^4 is hydrogen or C_{1-3} alkyl,

(e) —$CH(R^4)$—$PO(O^-)_2{\cdot}2M^+$,

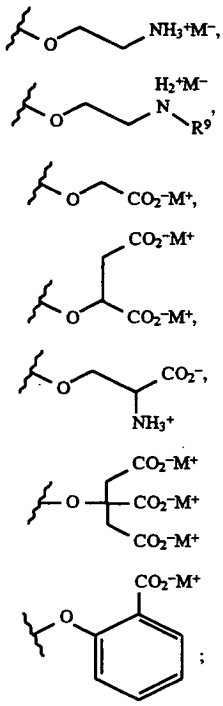
(f) —$CH(R^4)$—$PO(O^-)_2{\cdot}D^{2+}$,

(g) —$SO_3^-{\cdot}M+$,

(h) —$CH(R^4)$—$SO_3^-{\cdot}M^+$,

(i) —CO—CH_2CH_2—$CO_2^-{\cdot}M^+$,

(j) —CH(CH$_3$)—O—CO—R^5, wherein R^5 is selected from the group consisting of:



and

(k) hydrogen, with the proviso that if p is 0 and none of R^{11}, R^{12} or R^{13} are —OX, then X is other than hydrogen;

Y is selected from the group consisting of:

(1) a single bond,
(2) —O—,
(3) —S—,
(4) —CO—,
(5) —CH$_2$—,
(6) —CHR^{15}—, and
(7) —CR^{15}R^{16}—, wherein R^{15} and R^{16} are independently selected from the group consisting of:
  (a) C$_{1-6}$ alkyl, unsubstituted or substituted with one or more of the substituents selected from:
    (i) hydroxy,
    (ii) oxo,
    (iii) C$_{1-6}$ alkoxy,
    (iv) phenyl-C$_{1-3}$ alkoxy,
    (v) phenyl,
    (vi) —CN,
    (vii) halo,
    (viii) —NR^{9}R^{10}, wherein R^9 and R^{10} are as defined above,
    (ix) —NR^{9}COR^{10}, wherein R^9 and R^{10} are as defined above,
    (x) —NR^{9}CO$_2$R^{10}, wherein R^9 and R^{10} are as defined above,
    (xi) —CONR^{9}R^{10}, wherein R^9 and R^{10} are as defined above,
    (xii) —COR^9, wherein R^9 is as defined above, and
    (xiii) —CO$_2$R^9, wherein R^9 is as defined above;
  (b) phenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
    (i) hydroxy,
    (ii) C$_{1-6}$ alkoxy,
    (iii) C$_{1-6}$alkyl,
    (iv) C$_{2-5}$ alkenyl,
    (v) halo,
    (vi) —CN,
    (vii) —NO$_2$,
    (viii) —CF$_3$,
    (ix) —(CH$_2$)$_m$—NR^{9}R^{10}, wherein m, R^9 and R^{10} are as defined above,
    (x) —NR^{9}COR^{10}, wherein R^9 and R^{10} are as defined above,
    (xi) —NR^{9}CO$_2$R^{10}, wherein R^9 and R^{10} are as defined above,
    (xii) —CONR^{9}R^{10}, wherein R^9 and R^{10} are as defined above,
    (xiii) —CO$_2$NR^{9}R^{10}, wherein R^9 and R^{10} are as defined above,
    (xiv) —COR^9, wherein R^9 is as defined above, and
    (xv) —CO$_2$R^9, wherein R^9 is as defined above;

Z is selected from:

(1) hydrogen,
(2) C$_{1-6}$ alkyl, and
(3) hydroxy, with the proviso that if Y is —O—, Z is other than hydroxy, or if Y is —CHR^{15}—, then Z and R^{15} are optionally joined together to form a double bond.

The instant compounds are prodrugs of their parent compounds. A principal advantage of the instant compounds is that they possess enhanced solubility in aqueous solutions relative to their parent compounds. In addition, the prodrugs generally have diminished activity at antagonizing tachykinin receptors than their parent compounds. Thus, the activity exhibited upon administration of the prodrug is principally due to the presence of the parent compound that results from cleavage of the prodrug.

The term "prodrug" refers to compounds which are drug precursors which, following administration and absorption, release the drug in vivo via some metabolic process.

Prodrugs are entities structurally related to an biologically active substance (the "parent drug") which, after administration, release the parent drug in vivo as the result of some metabolic process, such as enzymatic or chemical hydrolysis of a carboxylic, phosphoric or sulfate ester or reduction or oxidation of a susceptible functionality (see, for example, discussions by (1) A. A. Sinkula and S. H. Yalkowsky, *J. Pharm. Sci,* 64, 181 (1975); (2) L. A. Sevensson, *Pharm Weekbl,* 122, 245–250 (1987); (3) L. P. Balant, E. Doelker and P. Buri *Eur. J. Drug Metab. and Pharmacokinetics,* 15, 143–153 (1990); (4) N. Bodor, *Drugs of the Future,* 6, 165–182 (1981); (5) *Design of Biopharmaceutical Properties through Prodrugs and Analogs.,* E. B. Roche, Ed., American Pharmaceutical Association Academy of Pharmaceutical Sciences, Washington, D.C., (1977); (6) H. Bundgaard *Advanced Drug Delivery Reviews,* 3, 39–65 (1989)). The advantage of a prodrug may lie in its physical properties, such as enhanced water solubility for parenteral administration compared to the parent drug, or it may enhance absorption from the digestive tract, or it may enhance drug stability for long-term storage. In general, a prodrug possesses less biological activity than its parent drug. A prodrug may also improve overall drug efficacy, for example, through the reduction of toxicity and unwanted effects of a drug by controlling its absorption, blood levels, metabolic distribution and cellular uptake.

The term "parent compound" or "parent drug" refers to the biologically active entity that is released via enzymatic action of a metabolic or a catabolic process, or via a chemical process following administration of the prodrug.

The parent compound may also be the starting material for the preparation of its corresponding prodrug.

While all of the usual routes of administration are useful with the present compounds, the preferred routes of administration are oral and intravenous. After gastrointestinal absorption or intravenous administration, the present compounds are hydrolyzed or otherwise cleaved in vivo to the corresponding parent compounds of formula I, wherein X is hydrogen or X is absent, or a salt thereof. Since the parent compounds may be relatively insoluble in aqueous solutions, the instant prodrugs provide a distinct advantage by virtue of their relatively enhanced aqueous solubility.

The compounds of the present invention have asymmetric centers and this invention includes all of the optical isomers and mixtures thereof.

In addition compounds with carbon-carbon double bonds may occur in Z– and E– forms with all isomeric forms of the compounds being included in the present invention.

When any variable (e.g., alkyl, aryl, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, etc.) occurs more than one time in any variable or in Formula I, its definition on each ocurrence is independent of its definition at every other occurrence.

As used herein, the term "alkyl" includes those alkyl groups of a designated number of carbon atoms of either a straight, branched, or cyclic configuration. Examples of "alkyl" include methyl, ethyl, propyl, isopropyl, butyl, iso-sec- and tert-butyl, pentyl, hexyl, heptyl, 3-ethylbutyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, and the like. "Alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge, such as methoxy, ethoxy, propoxy, butoxy and pentoxy. "Alkenyl" is intended to include hydrocarbon chains of a specified number of carbon atoms of either a straight- or branched-configuration and at least one unsaturation, which may occur at any point along the chain, such as ethenyl, propenyl, butenyl, pentenyl, dimethylpentyl, and the like, and includes E and Z forms, where applicable. "Halogen" or "halo", as used herein, means fluoro, chloro, bromo and iodo.

The compounds of the present invention are capable of forming salts with various inorganic and organic acids and bases and such salts are also within the scope of this invention. Examples of such acid addition salts (which are negative counterions defined herein as "M^-") include acetate, adipate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, citrate, ethanesulfonate, fumarate, hemisulfate, 2-hydroxyethylsulfonate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, lactate, malate, maleate, methanesulfonate, 2-naphthalenesulfonate, oxalate, pamoate, persulfate, picrate, pivalate, propionate, salicylate, stearate, succinate, surf ate, tartrate, tosylate (p-toluenesulfonate), and undecanoate. Base salts (which are pharmaceutically acceptable monovalent cations defined herein as "M^+ or K^+" or pharmaceutically acceptable divalent cations defined herein as "D^{2+}", if appropriate) include ammonium salts, alkali metal salts such as sodium, lithium and potassium salts, alkaline earth metal salts such as aluminum, calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, ornithine, and so forth. If M^+ is a monovalent cation, it is recognized that if the definition $2M^+$ is present, each of M^+ may be the same or different. In addition, it is similarly recognized that if the definition $2M^+$ is present, a divalent cation D^{2+} may instead be present. Also, the basic nitrogen-containing groups may be quaternized with such agents as: lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl; diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; aralkyl halides like benzyl bromide and others. The non-toxic physiologically acceptable salts are preferred, although other salts are also useful, such as in isolating or purifying the product.

The salts may be formed by conventional means, such as by reacting the free base form of the product with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is removed in vacuo or by freeze drying or by exchanging the anions of an existing salt for another anion on a suitable ion exchange resin.

In the compounds of formula I it is preferred that:

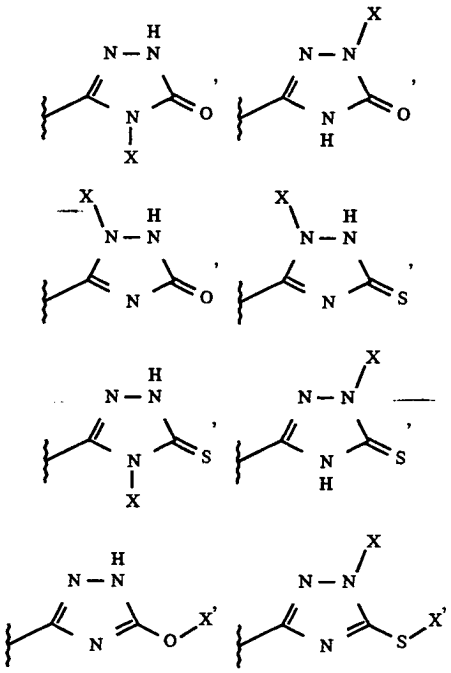
R^2 and R^3 are independently selected from the group consisting of:
(1) hydrogen,
(2) $C_{1\text{-}6}$ alkyl,
(3) $C_{2\text{-}6}$ alkenyl, and
(4) phenyl;

R^6, R^7 and R^8 are independently selected from the group consisting of:
(1) hydrogen,
(2) $C_{1\text{-}6}$ alkyl,
(3) fluoro,
(4) chloro,
(5) bromo,
(6) iodo, and
(7) $—CF_3$;

R^{11}, R^{12} and R^{13} are independently selected from the group consisting of:
(1) fluoro,
(2) chloro,
(3) bromo, and
(4) iodo;

A is unsubstituted $C_{1\text{-}6}$ alkyl;

B is selected from the group consisting of:



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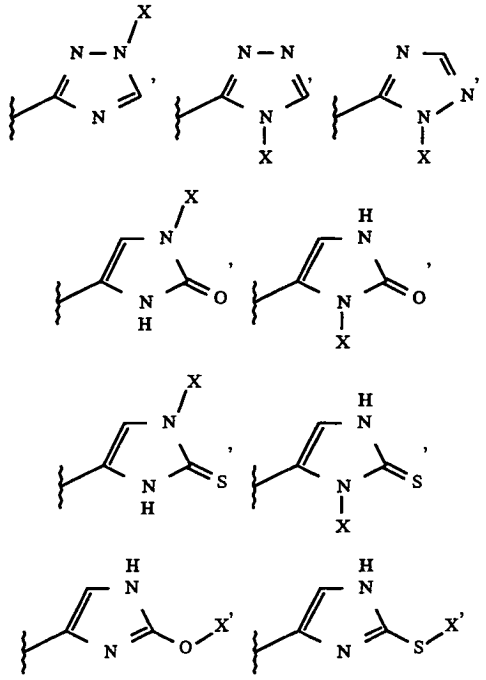


p is 0;

X is selected from:

(a) —PO(OH)O$^-$•M$^+$, wherein M$^+$ is a pharmaceutically acceptable monovalent counterion,

(b) —PO(O$^-$)$_2$•2M$^+$,

(c) —PO(O$^-$)$_2$•D^{2+}, wherein D^{2+} is a pharmaceutically acceptable divalent counterion,

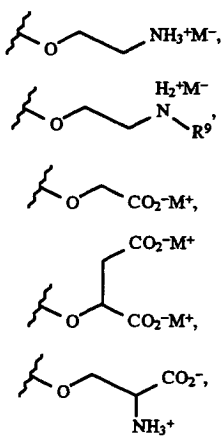
(d) —CH(R^4)—PO(OH)O$^-$•M$^+$, wherein R^4 is hydrogen or methyl,

(e) —CH(R^4)—PO(O$^-$)$_2$•2M$^+$, wherein R^4 is hydrogen or methyl,

(f) —CH(R^4)—PO(O$^-$)$_2$•D^{2+}, wherein R^4 is hydrogen or methyl,

(i) —CO—CH$_2$CH$_2$—CO$_2^-$•M$^+$,

(j) —CH(CH$_3$)—O—CO—R^5, wherein R^5 is selected from the group consisting of:



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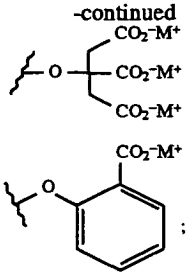


and

Y is —O—;

Z is hydrogen or C$_{1-4}$ alkyl.

In the compounds of the present invention a preferred embodiment includes those compounds wherein Z is C$_{1-4}$ alkyl. An especially preferred embodiment of the compounds of formula I includes those compounds wherein Z is —CH$_3$. These compounds bearing a substituent on the alpha-carbon atom exibit advantageous pharmacological properties, in particular, enhanced duration of action in models of extravasation, presumably due to biological stability and resistance to enzymatic degradation.

In the compounds of the present invention if p is 1, it is preferred that X is hydrogen or is absent.

In the compounds of the present invention a particularly preferred embodiment is that in which A is —CH$_2$— or —CH(CH$_3$)—.

A particularly preferred embodiment of the compounds of the present invention includes the prodrugs of compounds of formula I wherein —A—B is a (1,2,4-triazolo)methyl or a (5-oxo-1,2,4-triazolo)methyl group.

Another particularly preferred embodiment of the compounds of the present invention includes the prodrugs of compounds of formula I wherein —A—B is a (1,3-imidazolo)methyl or a (5-oxo-1,3-imidazolo)methyl group.

An additional particularly preferred embodiment of the compounds of the present invention includes those compounds of formula I wherein —A—B is a (1,2,4-triazolo) methyl or a (5-oxo-1,2,4-triazolo)methyl group beating a phosphoryl group attached to the heterocycle.

Yet another particularly preferred embodiment of the compounds of the present invention includes those compounds of formula I wherein —A—B is a (1,3-imidazolo) methyl or a (1,3-imidazolo)methyl group bearing a phosphoryl group attached to the heterocycle.

A preferred embodiment of the compounds of the present invention includes the compounds of formula I wherein X is selected from:

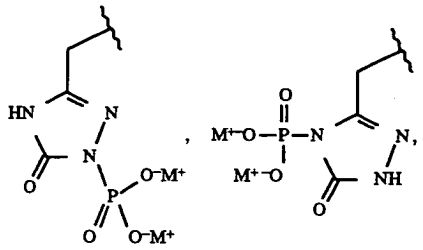
(a) —PO(O$^-$)$_2$•2M$^+$, wherein M$^+$ is a pharmaceutically acceptable monovalent counterion,

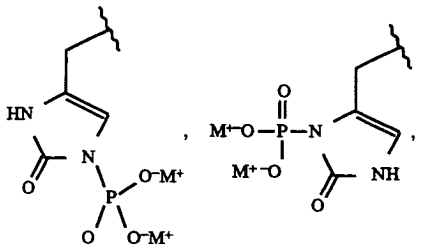
(b) —PO(O$^-$)$_2$•D^{2+}, wherein D^{2+} is a pharmaceutically acceptable divalent counterion,

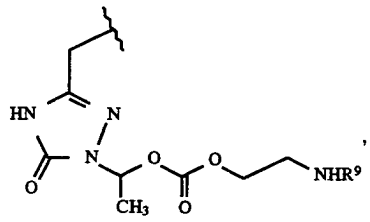
(c) —CH(CH$_3$)—O—CO—CH$_2$CH$_2$—NH$_3^+$•M$^-$, and

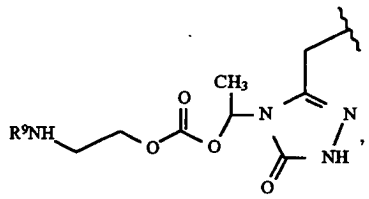
(d) —CH(CH$_3$)—O—CO—CH$_2$CH$_2$—NH$_2^+$—(CH$_2$CH$_2$—OH)•M$^-$.

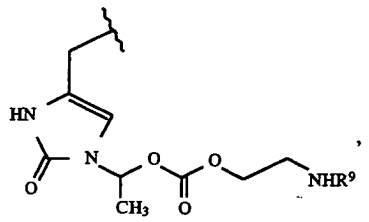
In the compounds of the present invention a particularly preferred embodiment is that in which —A—B is selected from the following group of substituents:

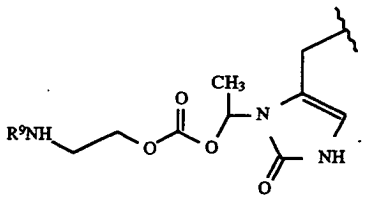












Specific compounds within the scope of the present invention include the prodrugs of the following parent compounds:

1) (±)-2-(3,5-bis(trifluoromethyl)benzyloxy)-3-phenylmorpholine;
2) (2R,S)-(3,5-bis(trifluoromethyl)benzyloxy)-(3R)-phenyl-(6R)-methyl-morpholine;
3) (2R,S)-(3,5-bis(trifluoromethyl)benzyloxy)-(3S)-phenyl-(6R)-methyl-morpholine;
4) (±)-2,(3,5-bis(trifluoromethyl)benzyloxy)-3-phenyl-4-methylcarboxamido-morpholine;
5) (±)-2-(3,5-bis(trifluoromethyl)benzyloxy)-3-phenyl-4-methoxycarbonylmethyl-morpholine;
6) 2-(2-(3,5-bis(trifluoromethyl)phenyl)ethenyl)-3-phenyl-5-oxo-morpholine;
7) 3-phenyl-2-(2-(3,5-bis(trifluoromethyl)phenyl)-ethyl) morpholine;
8) 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-6-(S)-methyl-morpholine;
9) 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-6-(S)-methyl-morpholine;
10) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-6-(S)-methyl-morpholine;
11) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-6-(S)-methyl-morpholine;
12) 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(R)-methyl-morpholine;
13) 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(R)-methyl-morpholine;
14) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(R)-methyl-morpholine;
15) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(R)-methyl-morpholine;
16) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-morpholine;
17) 4-(3-(1,2,4-triazolo)methyl)-2-(S)-(3,5-bis (trifluoromethyl)benzyloxy)-3-(S)-phenyl-morpholine;
18) 4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-morpholine;
19) 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-6-(R)-methyl-morpholine;
20) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-6-(R)-methyl-morpholine;
21) 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-6-(R)-methyl-morpholine;
22) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-6-(R)-methyl-morpholine;
23) 2-(R)-(3,5-bis(trifluoromethyl)-benzyloxy)-3-(S)-phenyl-5-(S)-methyl-morpholine;
24) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(S)-methyl-morpholine;
25) 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(S)-methyl-morpholine;
26) 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(R)-phenyl-morpholine;
27) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(R)-phenyl-morpholine;
28) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(S)-phenyl-morpholine;
29) 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(S)-phenyl-morpholine;
30) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-6-(R)-methyl-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;
31) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-6-(R)-methyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-3-(S)-phenyl-morpholine;
32) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenylmorpholine;
33) 4-(3-(1,2,4-triazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-morpholine;
34) 4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-2-(S)-(3,5-bis-(trifluoromethyl)benzyloxy)-3-(R)-phenyl-morpholine;
35) 4-(2-(imidazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-morpholine;
36) 4-(4-(imidazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl) benzyloxy)-3-(R)-phenyl-morpholine;
37) 4-(aminocarbonylmethyl)-2-(S)-(3,5-bis (trifluoromethyl)benzyloxy)-3-(R)-phenyl-morpholine;

38) 4-(2-(imidazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl) benzyloxy)-3-(S)-phenyl-morpholine;
39) 4-(4-(imidazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl) benzyloxy)-3-(S)-phenyl-morpholine;
40) 4-(2-(imidazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl) benzyloxy)-3-(S)-phenyl-6-(R)-methyl-morpholine;
41) 4-(4-(imidazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl) benzyloxy)-3-(S)-phenyl-6(R)-methyl-morpholine;
42) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-((6-hydroxy)-hexyl)-3-(R)-phenyl-morpholine;
43) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(5-(methylaminocarbonyl)pentyl)-3-(R)-phenyl -morpholine;
44) 4-(3-(1,2,4-triazolo)methyl)-2-(3,5-dimethylbenzyloxy) -3-phenylmorpholine;
45) 4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-2-(3,5-dimethyl)benzyloxy)-3-phenyl-morpholine;
46) 4-(3-(1,2,4-triazolo)methyl)-2-(3,5-di(tert-butyl) benzyloxy)-3-phenylmorpholine;
47) 4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-2-(3,5-di (tert-butyl)benzyloxy)-3-phenyl-morpholine;
48) 4-(3-(1,2,4-triazolo)methyl)-2-(3-(tert-butyl)-5-methylbenzyloxy)-3-phenyl-morpholine;
49) 4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-2-(3-(tert-butyl)-5-methylbenzyloxy)-3-phenyl-morpholine;
50) 4-(3-(1,2,4-triazolo)methyl)-2-(3-(trifluoro-methyl)-5-methyl-benzyloxy)-3-phenyl-morpholine;
51) 4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-2-(3-(trifluoromethyl)-5-methylbenzyloxy)-3-phenyl-morpholine;
52) 4-(3-(1,2,4-triazolo)methyl)-2-(3-(tert-butyl)-5-(trifluoromethyl)benzyloxy)-3-phenyl-morpholine;
53) 4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-2-(3-(tert-butyl)-5-(trifluoromethyl)benzyloxy)-3-phenyl-morpholine;
54) 4-(2-(imidazolo)methyl)-2-(3,5-dimethyl-benzyloxy)-3-phenyl-morpholine;
55) 4-(4-(imidazolo)methyl)-2-(3,5-dimethyl-benzyloxy)-3-phenyl-morpholine;
56) 4-(2-(imidazolo)methyl)-2-(3,5-di(tert-butyl)-benzyloxy)-3-phenyl-morpholine;
57) 4-(4-(imidazolo)methyl)-2-(3,5-di(tert-butyl)-benzyloxy)-3-phenyl-morpholine;
58) 4-(2-(imidazolo)methyl)-2-(3-(tert-butyl)-5-methylbenzyloxy)-3-phenyl-morpholine;
59) 4-(4-(imidazolo)methyl)-2-(3-(tert-butyl)-5-methylbenzyloxy)-3-phenyl-morpholine;
60) 4-(2-(imidazolo)methyl)-2-(3-(trifluoro-methyl)-5-methylbenzyloxy)-3-phenyl-morpholine;
61) 4-(4-(imidazolo)methyl)-2-(3-(trifluoro-methyl)-5-methylbenzyloxy)-3-phenyl-morpholine;
62) 4-(2-(imidazolo)methyl)-2-(3-(tert-butyl)-5-(trifluoromethyl)benzyloxy)-3-phenyl-morpholine;
63) 2-(S)-(3,5-dichlorobenzyloxy)-3-(S)-phenyl-morpholine;
64) 2-(S)-(3,5-dichlorobenzyloxy)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-3-(S)-phenylmorpholine;
65) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(methoxycarbonylmethyl)-3-(S)-phenyl-morpholine;
66) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(carboxymethyl)-3-(S)-phenyl-morpholine;
67) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-((2-aminoethyl)aminocabonylmethyl)-3-(S)-phenyl-morpholine;
68) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-((3-aminopropyl)amino carbonylmethyl)-3-(S)-phenylmorpholine;
69) 4-benzyl-5-(S),6-(R)-dimethyl-3-(S)-phenylmorpholinone and 4-benzyl-5-(R),6-(S)-dimethyl-3-(S)-phenyl-morpholinone;
70) 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-[5-(S),6-(R) or 5-(R),6-(S)-dimethyl]-3-(S)-phenyl-morpholinone;
71) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-[5-(R),6-(S) or 5-(S),6-(R)-dimethyl]-3-(S)-phenyl-morpholinone;
72) 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(3-(1,2,4-triazolo)methyl)-[5-(S),6-(R) or 5-(R),6-(S)-dimethyl]-3-(S)-phenyl-morpholinone;
73) 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(3-(5-oxo-1H,4H -1,2,4-triazolo)methyl)-[5-(S),6-(R) or 5-(R),6-(S) -dimethyl]-3-(S)-phenyl-morpholinone;
74) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(3-(1,2,4-triazolo)methyl)-[5-(R),6-(S) or 5-(S),6-(R)-dimethyl]-3-(S)-phenyl-morpholinone;
75) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-[5-(R),6-(S) or 5-(S),6-(R) -dimethyl]-3-(S)-phenyl-morpholinone;
76) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(2-(1-(4-benzyl)piperidino)ethyl)-3-(S)-phenyl-morpholine;
77) 3-(S)-(4-fluorophenyl)-4-benzyl-2-morpholinone;
78) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-(4-fluorophenyl)-4-benzyl-morpholine;
79) 2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-(4-fluorophenyl)morpholine;
80) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl-morpholine;
81) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-((3-pyridyl)methyl carbonyl)-3-(R)-phenyl-morpholine;
82) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(methoxycarbonylpentyl)-3-(R)-phenyl-morpholine;
83) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(carboxypentyl)-3-(R)-phenyl-morpholine;
84) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(methylaminocarbonylpentyl)-6-oxo-hexyl)-3-(R)-phenyl-morpholine;
85) 2-(R)-(3,5-bis(trifluoromethyl)benzoyloxy)-3-(S)-phenyl-4-benzyl-morpholine;
86) 2-(R)-(1-(3,5-bis(trifluoromethyl)phenyl)ethenyloxy)-3-(S)-phenyl-4-benzyl-morpholine;
87) 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-phenyl-morpholine;
88) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-phenyl-morpholine;
89) 2-(R)-(1-(S)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl-morpholine;
90) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl-morpholine;
91) 2-(R)-(3,5-bis(trifluoromethyl)benzoyloxy)-3-(S)-(4-fluoro)phenyl-4-benzyl-morpholine;
92) 2-(R)-(1-(3,5-bis(trifluoromethyl)phenyl)ethenyloxy)-3-(S)-(4-fluoro)phenyl-4-benzyl-morpholine;
93) 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;
94) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;
95) 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo) methylmorpholine;
96) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo) methylmorpholine;
97) 2-(R)-(1-(R)-(1-(3-(methyl)naphthyl))ethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

98) 2-(R)-(1-(R)-(1-(3-(methyl)naphthyl))ethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl-morpholine;

99) 2-(R)-(1-(R)-(3-(fluoro)-5-(trifluoromethyl)phenyl) ethoxy)-3-(S)-phenyl-morpholine;

100) 2-(R)-(1-(R)-(3-(fluoro)-5-(trifluoromethyl)phenyl) ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo) methyl)morpholine;

101) 2-(R)-(1-(R)-(3-(chloro)-5-(trifluoromethyl)phenyl) ethoxy)-3-(S)-phenyl-morpholine;

102) 2-(R)-(1-(R)-(3-(chloro)-5-(trifluoromethyl)phenyl) ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo) methyl)morpholine;

103) 2-(R)-(1-(R)-(3,5-(dimethyl)phenyl)ethoxy)-3-(S)-phenylmorpholine;

104) 2-(R)-(1-(R)-(3,5-(dimethyl)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;

105) 2-(R)-(1-(R)-(3-(fluoro)-5-(methyl)phenyl)ethoxy)-3-(S)-phenylmorpholine;

106) 2-(R)-(1-(R)-(3-(fluoro)-5-(methyl)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;

107) 2-(R)-(1-(R)-(3-(chloro)-5-(methyl)phenyl)ethoxy)-3-(S)-phenyl-morpholine;

108) 2-(R)-(1-(R)-(3-(chloro)-5-(methyl)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;

109) 2-(R)-(1-(R)-(3-(bromo)-5-(methyl)phenyl)ethoxy)-3-(S)-phenyl-morpholine;

110) 2-(R)-(1-(R)-(3-(bromo)-5-(methyl)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;

111) 2-(R)-(1-(R)-(3-(isopropoxy)phenyl)ethoxy)-3-(S)-phenylmorpholine;

112) 2-(R)-(1-(R)-(3-(isopropoxy)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;

113) 2-(R)-(1-(R)-(3-(isopropoxy)-5-trifluoromethyl) phenyl)ethoxy)-3-(S)-phenyl-morpholine;

114) 2-(R)-(1-(R)-(3-(isopropoxy)-5-trifluoromethyl) phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine;

115) 2-(R)-(1-(R)-(3-(chloro)-5-(isopropoxy)phenyl) ethoxy)-3-(S)-phenyl-morpholine;

116) 2-(R)-(1-(R)-(3-(chloro)-5-(isopropoxy)phenyl) ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo) methyl)-morpholine;

117) 2-(R)-(1-(R)-(3-(fluoro)-5-(isopropoxy)phenyl) ethoxy)-3-(S)-phenyl-morpholine;

118) 2-(R)-(1-(R)-(3-(fluoro)-5-(isopropoxy)phenyl) ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo) methyl)-morpholine;

119) 2-(R)-(1-(R)-(1-(3-(trifluoromethyl)naphthyl))ethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

120) 2-(R)-(1-(R)-(1-(3-(trifluoromethyl)naphthyl))ethoxy) -3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

121) 2-(R)-(1-(R)-(3-(t-butyl)-5-(chloro)phenyl) ethoxy)-3-(S)-phenylmorpholine;

122) 2-(R)-(1-(R)-(3-(t-butyl)-5-(chloro)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;

123) 2-(R)-(1-(R)-(3-(t-butyl)-5-(trifluoromethyl)phenyl) ethoxy)-3-(S)-phenyl-morpholine;

124) 2-(R)-(1-(R)-(3-(t-butyl)-5-(trifluoromethyl)phenyl) ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo) methyl)morpholine;

125) 2-(R)-(1-(R)-(3,5-(dimethyl)-4-(fluoro)phenyl)ethoxy) -3-(S)-phenyl-morpholine;

126) 2-(R)-(1-(R)-(3,5-(dimethyl)-4-(fluoro)phenyl)ethoxy) -3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;

127) 2-(R)-(1-(R)-(3,5-(dimethyl)-4-(chloro)phenyl)ethoxy) -3-(S)-phenyl-morpholine;

128) 2-(R)-(1-(R)-(3,5-(dimethyl)-4-(chloro)phenyl)ethoxy) -3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;

129) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-4-(fluoro) phenyl)ethoxy)-3-(S)-phenyl-morpholine;

130) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-4-(fluoro) phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine;

131) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-4-chloro) phenyl)ethoxy)-3-(S)-phenyl-morpholine;

132) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-4-chloro) phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine;

133) 2-(R)-(1-(R)-(3,5-(dichloro)phenyl)ethoxy)-3-(S)-phenylmorpholine;

134) 2-(R)-(1-(R)-(3,5-(dichloro)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;

135) 2-(R)-(1-(R)-(3,5-(difluoro)phenyl)ethoxy)-3-(S)-phenylmorpholine;

136) 2-(R)-(1-(R)-(3,5-(difluoro)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;

137) 2-(R)-(1-(R)-(1-(naphthyl)ethoxy)-3-(S)-phenyl-morpholine;

138) 2-(R)-(1-(R)-(1-(naphthyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methylmorpholine;

139) 2-(R)-(1-(R)-(1-(4-(fluoro)naphthyl))ethoxy)-3-(S)-phenylmorpholine;

140) 2-(R)-(1-(R)-(1-(4-(fluoro)naphthyl))ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;

141) 2-(R)-(1-(R)-(1-(3-(fluoro)naphthyl))ethoxy)-3-(S)-phenylmorpholine;

142) 2-(R)-(1-(R)-(1-(3-(fluoro)naphthyl))ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;

143) 2-(R)-(1-(R)-(1-(3-(chloro)naphthyl))ethoxy)-3-(S)-phenylmorpholine;

144) 2-(R)-(1-(R)-(1-(3-chloro)naphthyl))ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;

145) 2-(R)-(1-(R)-(1-(3-(methyl)naphthyl))ethoxy)-3-(S)-phenylmorpholine;

146) 2-(R)-(1-(R)-(1-(3-(methyl)naphthyl))ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;

147) 2-(R)-(1-(R)-(1-(3-(trifluoromethyl)naphthyl))ethoxy) -3-(S)-phenyl-morpholine;

148) 2-(R)-(1-(R)-(1-(3-(trifluoromethyl)naphthyl))ethoxy) -3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;

149) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-(4-hydroxy)phenyl-morpholine;

150) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-(4-hydroxy)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo) methyl)-morpholine;

151) 2-(S)-(2-fluoro-5-trifluoromethyl)benzyloxy-3-(S)-phenylmorpholine;

152) 2-(S)-(2-fluoro-5-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro)phenyl-morpholine;

153) 2-(R)-(1-(R)-(2-fluoro-5-trifluoromethyl) phenylethoxy)-3-(S)-phenyl-morpholine;

154) 2-(R)-(1-(R)-(2-fluoro-5-trifluoromethyl) phenylethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;

155) 2-(S)-(2-fluoro-5-trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

156) 2-(S)-(2-fluoro-5-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

157) 2-(R)-(1-(R)-(2-fluoro-5-trifluoromethyl) phenylethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl) -morpholine;

158) 2-(R)-(1-(R)-(2-fluoro-5-trifluoromethyl) phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

159) 2-(S)-(2-fluoro-5-trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;

160) 2-(S)-(2-fluoro-5-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl) morpholine;

161) 2-(R)-(1-(R)-(2-fluoro-5-trifluoromethyl) phenylethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;

162) 2-(R)-(1-(R)-(2-fluoro-5-trifluoromethyl) phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H, 4H-1,2,4-triazolo)methyl)morpholine;

163) 2-(S)-(2-fluoro-5-trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

164) 2-(S)-(2-fluoro-5-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

165) 2-(R)-(1-(R)-(2-fluoro-5-trifluoromethyl) phenylethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo) methyl)-morpholine;

166) 2-(R)-(1-(R)-(2-fluoro-5-trifluoromethyl) phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

167) 2-(S)-(2-fluoro-5-trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(2-imidazolo)methyl-morpholine;

168) 2-(S)-(2-fluoro-5-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(2-imidazolo)methyl-morpholine;

169) 2-(R)-(1-(R)-(2-fluoro-5-trifluoromethyl) phenylethoxy)-3-(S)-phenyl-4-(2-imidazolo)methyl-morpholine;

170) 2-(R)-(1-(R)-(2-fluoro-5-trifluoromethyl) phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(2-imidazolo) methyl-morpholine;

171) 2-(S)-(2-fluoro-5-trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(4-imidazolo)methyl-morpholine;

172) 2-(S)-(2-fluoro-5-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(4-imidazolo)methyl-morpholine;

173) 2-(R)-(1-(R)-(2-fluoro-5-trifluoromethyl) phenylethoxy)-3-(S)-phenyl-4-(4-imidazolo)methyl-morpholine;

174) 2-(R)-(1-(R)-(2-fluoro-5-trifluoromethyl) phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-imidazolo) methyl-morpholine;

175) 2-(S)-(2-fluoro-5-trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(5-tetrazolo)methyl-morpholine;

176) 2-(S)-(2-fluoro-5-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(5-tetrazolo)methyl-morpholine;

177) 2-(R)-(1-(R)-(2-fluoro-5-trifluoromethyl) phenylethoxy)-3-(S)-phenyl-4-(5-tetrazolo)methyl-morpholine;

178) 2-(R)-(1-(R)-(2-fluoro-5-trifluoromethyl) phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(5-tetrazolo) methyl-morpholine;

179) 2-(S)-(2-fluoro-5-trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;

180) 2-(S)-(2-fluoro-5-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;

181) 2-(R)-(1-(R)-(2-fluoro-5-trifluoromethyl) phenylethoxy)-3-(S)-phenyl-4-(2-oxo-5H-pyrrol-4-yl) methyl-morpholine;

182) 2-(R)-(1-(R)-(2-fluoro-5-trifluoromethyl) phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;

183) 2-(S)-(2-chloro-5-trifluoromethyl)benzyloxy-3-(S)-phenylmorpholine;

184) 2-(S)-(2-chloro-5-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro)phenyl-morpholine;

185) 2-(R)-(1-(R)-(2-chloro-5-trifluoromethyl) phenylethoxy)-3-(S)-phenyl-morpholine;

186) 2-(R)-(1-(R)-(2-chloro-5-trifluoromethyl) phenylethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;

187) 2-(S)-(2-chloro-5-trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

188) 2-(S)-(2-chloro-5-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

189) 2-(R)-(1-(R)-(2-chloro-5-trifluoromethyl) phenylethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl) -morpholine;

190) 2-(R)-(1-(R)-(2-chloro-5-trifluoromethyl) phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

191) 2-(S)-(2-chloro-5-trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;

192) 2-(S)-(2-chloro-5-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl) morpholine;

193) 2-(R)-(1-(R)-(2-chloro-5-trifluoromethyl) phenylethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;

194) 2-(R)-(1-(R)-(2-chloro-5-trifluoromethyl) phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H, 4H-1,2,4-triazolo)methyl)morpholine;

195) 2-(S)-(2-chloro-5-trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

196) 2-(S)-(2-chloro-5-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

197) 2-(R)-(1-(R)-(2-chloro-5-trifluoromethyl) phenylethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo) methyl)-morpholine;

198) 2-(R)-(1-(R)-(2-chloro-5-trifluoromethyl) phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

199) 2-(S)-(2-chloro-5-trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(2-imidazolo)methyl)-morpholine;

200) 2-(S)-(2-chloro-5-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(2-imidazolo)methyl)-morpholine;

201) 2-(R)-(1-(R)-(2-chloro-5-trifluoromethyl) phenylethoxy)-3-(S)-phenyl-4-(2-imidazolo)methyl)-morpholine;

202) 2-(R)-(1-(R)-(2-chloro-5-trifluoromethyl) phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(2-imidazolo) methyl)-morpholine;

203) 2-(S)-(2-chloro-5-trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(4-imidazolo)methyl)-morpholine;

204) 2-(S)-(2-chloro-5-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(4-imidazolo)methyl-morpholine;

205) 2-(R)-(1-(R)-(2-chloro-5-trifluoromethyl) phenylethoxy)-3-(S)-phenyl-4-(4-imidazolo)methyl-morpholine;

206) 2-(R)-(1-(R)-(2-chloro-5-trifluoromethyl) phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-imidazolo) methyl-morpholine;

207) 2-(S)-(2-chloro-5-trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(5-tetrazolo)methyl-morpholine;

208) 2-(S)-(2-chloro-5-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(5-tetrazolo)methyl-morpholine;

209) 2-(R)-(1-(R)-(2-chloro-5-trifluoromethyl) phenylethoxy)-3-(S)-phenyl-4-(5-tetrazolo)methyl-morpholine;

210) 2-(R)-(1-(R)-(2-chloro-5-trifluoromethyl) phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(5-tetrazolo) methyl-morpholine;

211) 2-(S)-(2-chloro-5-trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;

212) 2-(S)-(2-chloro-5-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;

213) 2-(R)-(1-(R)-(2-chloro-5-trifluoromethyl) phenylethoxy)-3-(S)-phenyl-4-(2-oxo-5 H -pyrrol-4-yl) methyl-morpholine;

214) 2-(R)-(1-(R)-(2-Chloro-5-trifluoromethyl) phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;

215) 2-(S)-(3-methyl)benzyloxy-3-(S)-phenyl-morpholine;

216) 2-(S)-(3-methyl)benzyloxy-3-(S)-(4-fluoro)phenyl-morpholine;

217) 2-(R)-(1-(R)-(3-methyl)phenylethoxy)-3-(S)-phenyl-morpholine;

218) 2-(R)-(1-(R)-(3-methyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;

219) 2-(S)-(3-methyl)benzyloxy-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

220) 2-(S)-(3-methyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

221) 2-(R)-(1-(R)-(3-methyl)phenylethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

222) 2-(R)-(1-(R)-(3-methyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

223) 2-(S)-(3-methyl)benzyloxy-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl)-morpholine;

224) 2-(S)-(3-methyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl)-morpholine;

225) 2-(R)-(1-(R)-(3-methyl)phenylethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl)-morpholine;

226) 2-(R)-(1-(R)-(3-methyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl)-morpholine;

227) 2-(S)-(3-methyl)benzyloxy-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

228) 2-(S)-(3-methyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

229) 2-(R)-(1-(R)-(3-methyl)phenylethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

230) 2-(R)-(1-(R)-(3-methyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

231) 2-(S)-(3-methyl)benzyloxy-3-(S)-phenyl-4-(2-imidazolo)methylmorpholine;

232) 2-(S)-(3-methyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(2-imidazolo)methyl-morpholine;

233) 2-(R)-(1-(R)-(3-methyl)phenylethoxy)-3-(S)-phenyl-4-(2-imidazolo)methyl-morpholine;

234) 2-(R)-(1-(R)-(3-methyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(2-imidazolo)methyl-morpholine;

235) 2-(S)-(3-methyl)benzyloxy-3-(S)-phenyl-4-(4-imidazolo)methyl-morpholine;

236) 2-(S)-(3-methyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(4-imidazolo)methyl-morpholine;

237) 2-(R)-(1-(R)-(3-methyl)phenylethoxy)-3-(S)-phenyl-4-(4-imidazolo)methyl-morpholine;

238) 2-(R)-(1-(R)-(3-methyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-imidazolo)methyl-morpholine;

239) 2-(S)-(3-methyl)benzyloxy-3-(S)-phenyl-4-(5-tetrazolo)methyl-morpholine;

240) 2-(S)-(3-methyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(5-tetrazolo)methyl-morpholine;

241) 2-(R)-(1-(R)-(3-methyl)phenylethoxy)-3-(S)-phenyl-4-(5-tetrazolo)methyl-morpholine;

242) 2-(R)-(1-(R)-(3-methyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(5-tetrazolo)methyl-morpholine;

243) 2-(S)-(3-methyl)benzyloxy-3-(S)-phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;

244) 2-(S)-(3-methyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;

245) 2-(R)-(1-(R)-(3-methyl)phenylethoxy)-3-(S)-phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;

246) 2-(R)-(1-(R)-(3-methyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;

247) 2-(S)-(3-bromo)benzyloxy-3-(S)-phenyl-morpholine;

248) 2-(S)-(3-bromo)benzyloxy-3-(S)-(4-fluoro)phenyl-morpholine;

249) 2-(R)-(1-(R)-(3-bromo)phenylethoxy)-3-(S)-phenyl-morpholine;

250) 2-(R)-(1-(R)-(3-bromo)phenylethoxy)-3-(S)-(4-fluoro) phenyl-morpholine;

251) 2-(S)-(3-bromo)benzyloxy-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

252) 2-(S)-(3-bromo)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

253) 2-(R)-(1-(R)-(3-bromo)phenylethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

254) 2-(R)-(1-(R)-(3-bromo)phenylethoxy)-3-(S)-(4-fluoro) phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

255) 2-(S)-(3-bromo)benzyloxy-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl-morpholine;

256) 2-(S)-(3-bromo)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl-morpholine;

257) 2-(R)-(1-(R)-(3-bromo)phenylethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4Ho 1,2,4-triazolo)methyl)-morpholine;

258) 2-(R)-(1-(R)-(3-bromo)phenylethoxy)-3-(S)-(4-fluoro) phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;

259) 2-(S)-(3-bromo)benzyloxy-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

260) 2-(S)-(3-bromo)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

261) 2-(R)-(1-(R)-(3-bromo)phenylethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

262) 2-(R)-(1-(R)-(3-bromo)phenylethoxy)-3-(S)-(4-fluoro) phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

263) 2-(S)-(3-bromo)benzyloxy-3-(S)-phenyl-4-(2-imidazolo)methyl-morpholine;

264) 2-(S)-(3-bromo)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(2-imidazolo)methyl-morpholine;

265) 2-(R)-(1-(R)-(3-bromo)phenylethoxy)-3-(S)-phenyl-4-(2-imidazolo)methyl-morpholine;

266) 2-(R)-(1-(R)-(3-bromo)phenylethoxy)-3-(S)-(4-fluoro) phenyl-4-(2-imidazolo)methyl-morpholine;

267) 2-(S)-(3-bromo)benzyloxy-3-(S)-phenyl-4-(4-imidazolo)methyl-morpholine;

268) 2-(S)-(3-bromo)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(4-imidazolo)methyl-morpholine;

269) 2-(R)-(1-(R)-(3-bromo)phenylethoxy)-3-(S)-phenyl-4-(4-imidazolo)methyl-morpholine;
270) 2-(R)-(1-(R)-(3-bromo)phenylethoxy)-3-(S)-(4-fluoro) phenyl-4-(4-imidazolo)methyl-morpholine;
271) 2-(S)-(3-bromo)benzyloxy-3-(S)-phenyl-4-(5-tetrazolo)methyl-morpholine;
272) 2-(S)-(3-bromo)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(5-tetrazolo)methyl-morpholine;
273) 2-(R)-(1-(R)-(3-bromo)phenylethoxy)-3-(S)-phenyl-4-(5-tetrazolo)methyl-morpholine;
274) 2-(R)-(1-(R)-(3-bromo)phenylethoxy)-3-(S)-(4-fluoro) phenyl-4-(5-tetrazolo)methyl-morpholine;
275) 2-(S)-(3-bromo)benzyloxy-3-(S)-phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;
276) 2-(S)-(3-bromo)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;
277) 2-(R)-(1-(R)-(3-bromo)phenylethoxy)-3-(S)-phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;
278) 2-(R)-(1-(R)-(3-bromo)phenylethoxy)-3-(S)-(4-fluoro) phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;
279) 2-(S)-(3-chloro)benzyloxy-3-(S)-phenyl-morpholine;
280) 2-(S)-(3-chloro)benzyloxy-3-(S)-(4-fluoro)phenyl-morpholine;
281) 2-(R)-(1-(R)-(3-chloro)phenylethoxy)-3-(S)-phenyl-morpholine;
282) 2-(R)-(1-(R)-(3-chloro)phenylethoxy)-3-(S)-(4-fluoro) phenyl-morpholine;
283) 2-(S)-(3-chloro)benzyloxy-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;
284) 2-(S)-(3-chloro)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;
285) 2-(R)-(1-(R)-(3-chloro)phenylethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;
286) 2-(R)-(1-(R)-(3-chloro)phenylethoxy)-3-(S)-(4-fluoro) phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;
287) 2-(S)-(3-chloro)benzyloxy-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;
288) 2-(S)-(3-chloro)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;
289) 2-(R)-(1-(R)-(3-chloro)phenylethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;
290) 2-(R)-(1-(R)-(3-chloro)phenylethoxy)-3-(S)-(4-fluoro) phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;
291) 2-(S)-(3-chloro)benzyloxy-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;
292) 2-(S)-(3-chloro)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;
293) 2-(R)-(1-(R)-(3-chloro)phenylethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;
294) 2-(R)-(1-(R)-(3-chloro)phenylethoxy)-3-(S)-(4-fluoro) phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;
295) 2-(S)-(3-chloro)benzyloxy-3-(S)-phenyl-4-(2-imidazolo)methyl-morpholine;
296) 2-(S)-(3-chloro)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(2-imidazolo)methyl-morpholine;
297) 2-(R)-(1-(R)-(3-chloro)phenylethoxy)-3-(S)-phenyl-4-(2-imidazolo)methyl-morpholine;
298) 2-(R)-(1-(R)-(3-chloro)phenylethoxy)-3-(S)-(4-fluoro) phenyl-4-(2-imidazolo)methyl-morpholine;
299) 2-(S)-(3-chloro)benzyloxy-3-(S)-phenyl-4-(4-imidazolo)methyl-morpholine;
300) 2-(S)-(3-chloro)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(4-imidazolo)methyl-morpholine;
301) 2-(R)-(1-(R)-(3-chloro)phenylethoxy)-3-(S)-phenyl-4-(4-imidazolo)methyl-morpholine;
302) 2-(R)-(1-(R)-(3-chloro)phenylethoxy)-3-(S)-(4-fluoro) phenyl-4-(4-imidazolo)methyl-morpholine;
303) 2-(S)-(3-chloro)benzyloxy-3-(S)-phenyl-4-(5-tetrazolo)methyl-morpholine;
304) 2-(S)-(3-chloro)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(5-tetrazolo)methyl-morpholine;
305) 2-(R)-(1-(R)-(3-chloro)phenylethoxy)-3-(S)-phenyl-4-(5-tetrazolo)methyl-morpholine;
306) 2-(R)-(1-(R)-(3-chloro)phenylethoxy)-3-(S)-(4-fluoro) phenyl-4-(5-tetrazolo)methyl-morpholine;
307) 2-(S)-(3-chloro)benzyloxy-3-(S)-phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;
308) 2-(S)-(3-chloro)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;
309) 2-(R)-(1-(R)-(3-chloro)phenylethoxy)-3-(S)-phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;
310) 2-(R)-(1-(R)-(3-chloro)phenylethoxy)-3-(S)-(4-fluoro) phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;
311) 2-(S)-(3-trifluoromethyl)benzyloxy-3-(S)-phenyl-morpholine;
312) 2-(S)-(3-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro) phenyl-morpholine;
313) 2-(R)-(1-(R)-(3-trifluoromethyl)phenylethoxy)-3-(S)-phenyl-morpholine;
314) 2-(R)-(1-(R)-(3-trifluoromethyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;
315) 2-(S)-(3-trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(3-1H,4H-1,2,4-triazolo)methyl-morpholine;
316) 2-(S)-(3-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro) phenyl-4-(3-1H,4H-1,2,4-triazolo)methyl-morpholine;
317) 2-(R)-(1-(R)-(3-trifluoromethyl)phenylethoxy)-3-(S)-phenyl-4-(3-1H,4H-1,2,4-triazolo)methyl-morpholine;
318) 2-(R)-(1-(R)-(3-trifluoromethyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;
319) 2-(S)-(3-trifluoromethyl)benzyl oxy-3-(S)-phenyl-4-(3-(5-oxo)-1H,4H-1,2,4-triazolo)methyl)-morpholine;
320) 2-(S)-(3-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro) phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;
321) 2-(R)-(1-(R)-(3-trifluoromethyl)phenylethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;
322) 2-(R)-(1-(R)-(3-trifluoromethyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo) methyl)-morpholine;
323) 2-(S)-(3-trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;
324) 2-(S)-(3-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro) phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;
325) 2-(R)-(1-(R)-(3-trifluoromethyl)phenylethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;
326) 2-(R)-(1-(R)-(3-trifluoromethyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;
327) 2-(S)-(3-trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(2-imidazolo)methyl-morpholine;
328) 2-(S)-(3-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro) phenyl-4-(2-imidazolo)methyl-morpholine;
329) 2-(R)-(1-(R)-(3-trifluoromethyl)phenylethoxy)-3-(S)-phenyl-4-(2-imidazolo)methyl-morpholine;
330) 2-(R)-(1-(R)-(3-trifluoromethyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(2-imidazolo)methyl-morpholine;
331) 2-(S)-(3-trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(4-imidazolo)methyl-morpholine;
332) 2-(S)-(3-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro) phenyl-4-(4-imidazolo)methyl-morpholine;
333) 2-(R)-(1-(R)-(3-trifluoromethyl)phenylethoxy)-3-(S)-phenyl-4-(4-imidazolo)methyl-morpholine;
334) 2-(R)-(1-(R)-(3-trifluoromethyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-imidazolo)methyl-morpholine;

335) 2-(S)-(3-trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(5-tetrazolo)methyl-morpholine;
336) 2-(S)-(3-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro) phenyl-4-(5-tetrazolo)methyl-morpholine;
337) 2-(R)-(1-(R)-(3-trifluoromethyl)phenylethoxy)-3-(S)-phenyl-4-(5-tetrazolo)methyl-morpholine;
338) 2-(R)-(1-(R)-(3-trifluoromethyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(5-tetrazolo)methyl-morpholine;
339) 2-(S)-(3-trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;
340) 2-(S)-(3-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro) phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;
341) 2-(R)-(1-(R)-(3-trifluoromethyl)phenylethoxy)-3-(S)-phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;
342) 2-(R)-(1-(R)-(3-trifluoromethyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;
343) 2-(S)-(3-t-butyl)benzyloxy-3-(S)-phenyl-morpholine;
344) 2-(S)-(3-t-butyl)benzyloxy-3-(S)-(4-fluoro)phenyl-morpholine;
345) 2-(R)-(1-(R)-(3-t-butyl)phenylethoxy)-3-(S)-phenyl-morpholine;
346) 2-(R)-(1-(R)-(3-t-butyl)phenylethoxy)-3-(S)-(4-fluoro) phenyl-morpholine;
347) 2-(S)-(3-t-butyl)benzyloxy-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;
348) 2-(S)-(3-t-butyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;
349) 2-(R)-(1-(R)-(3-t-butyl)phenylethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;
350) 2-(R)-(1-(R)-(3-t-butyl)phenylethoxy)-3-(S)-(4-fluoro) phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;
351) 2-(S)-(3-t-butyl)benzyloxy-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl-morpholine;
352) 2-(S)-(3-t-butyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl-morpholine;
353) 2-(R)-(1-(R)-(3-t-butyl)phenylethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;
354) 2-(R)-(1-(R)-(3-t-butyl)phenylethoxy)-3-(S)-(4-fluoro) phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;
355) 2-(S)-(3-t-butyl)benzyloxy-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl-morpholine;
356) 2-(S)-(3- t-butyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl-morpholine;
357) 2-(R)-(1-(R)-(3-t-butyl)phenylethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl-morpholine;
358) 2-(R)-(1-(R)-(3-t-butyl)phenylethoxy)-3-(S)-(4-fluoro) phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl-morpholine;
359) 2-(S)-(3-t-butyl)benzyloxy-3-(S)-phenyl-4-(2-imidazolo)methyl-morpholine;
360) 2-(S)-(3-t-butyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(2-imidazolo)methyl-morpholine;
361) 2-(R)-(1-(R)-(3-t-butyl)phenylethoxy)-3-(S)-phenyl-4-(2-imidazolo)methyl-morpholine;
362) 2-(R)-(1-(R)-(3-t-butyl)phenylethoxy)-3-(S)-(4-fluoro) phenyl-4-(2-imidazolo)methyl-morpholine;
363) 2-(S)-(3-t-butyl)benzyloxy-3-(S)-phenyl-4-(4-imidazolo)methyl-morpholine;
364) 2-(S)-(3-t-butyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(4-imidazolo)methyl-morpholine;
365) 2-(R)-(1-(R)-(3-t-butyl)phenylethoxy)-3-(S)-phenyl-4-(4-imidazolo)methyl-morpholine;
366) 2-(R)-(1-(R)-(3-t-butyl)phenylethoxy)-3-(S)-(4-fluoro) phenyl-4-(4-imidazolo)methyl-morpholine;
367) 2-(S)-(3-t-butyl)benzyloxy-3-(S)-phenyl-4-(5-tetrazolo)methyl-morpholine;
368) 2-(S)-(3-t-butyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(5-tetrazolo)methyl-morpholine;
369) 2-(R)-(1-(R)-(3-t-butyl)phenylethoxy)-3-(S)-phenyl-4-(5-tetrazolo)methyl-morpholine;
370) 2-(R)-(1-(R)-(3-t-butyl)phenylethoxy)-3-(S)-(4-fluoro) phenyl-4-(5-tetrazolo)methyl-morpholine;
371) 2-(S)-(3-t-butyl)benzyloxy-3-(S)-phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;
372) 2-(S)-(3-t-butyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;
373) 2-(R)-(1-(R)-(3-t-butyl)phenylethoxy)-3-(S)-phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;
374) 2-(R)-(1-(R)-(3-t-butyl)phenylethoxy)-3-(S)-(4-fluoro) phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;
375) 4-(4-(imidazolo)methyl)-2-(3-(tert-butyl)-5-(trifluoromethyl)benzyloxy)-3-phenyl-morpholine;
376) 2-(R)-(2,5-bis(trifluoromethyl)benzoyloxy)-3-(S)-(4-fluorophenyl)-4-benzyl-morpholine;
377) 2-(R)-(1-(2,5-bis(trifluoromethyl)phenyl)ethenyloxy)-3-(S)-(4-fluorophenyl)-4-benzyl-morpholine;
378) 2-(R)-(1-(R)-(2,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-morpholine;
379) 2-(R)-(1-(R)-(2,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine;
380) 2-(R)-(1-(R)-(2,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(1,2,4-triazolo)methyl)-morpholine;
381) 2-(R)-(1-(R)-(2,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(4-(2-oxo-1,3-imidazolo) methyl)-morpholine;
382) 2-(R)-(1-(R)-(3-(thiomethyl)phenyl)ethoxy)-3-(S)-phenyl-morpholine;
383) 2-(R)-(1-(R)-(3-(thiomethylphenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;
384) 2-(R)-(1-(R)-(3-(thiomethylphenyl)ethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;
385) 2-(R)-(1-(R)-(3-(thiomethylphenyl)ethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;
386) 2-(R)-(1-(R)-(3-(thiomethyl)-5-(trifluoromethyl) phenyl)ethoxy)-3-(S)-phenyl-morpholine;
387) 2-(R)-(1-(R)-(3-(thiomethyl-5-(trifluoromethyl) phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;
388) 2-(R)-(1-(R)-(3-(thiomethyl-5-(trifluoromethyl) phenyl)ethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo) methyl)-morpholine;
389) 2-(R)-(1-(R)-(3-(thiomethyl-5-(trifluoromethyl) phenyl)ethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo) methyl)-morpholine;
390) 2-(R)-(1-(R)-(2,2-(dimethyl)-5-(thiomethyl)-2,3-dihydrobenzofuran-7-yl)ethoxy)-3-(S)-phenyl-morpholine;
391) 2-(R)-(1-(R)-(2,2-(dimethyl)-5-(thiomethyl)-2,3-dihydrobenzofuran-7-yl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;
392) 2-(R)-(1-(R)-(2,2-(dimethyl)-5-(thio methyl)-2,3-dihydrobenzofuran-7-yl)ethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;
393) 2-(R)-(1-(R)-(2,2-(dimethyl)-5-(thiomethyl)-2,3-dihydrobenzofuran-7-yl)ethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;
394) 2-(R)-(1-(R)-(3,5-(dimethoxy)phenyl)ethoxy)-3-(S)-phenylmorpholine;
395) 2-(R)-(1-(R)-(3,5-(dimethoxy)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;

396) 2-(R)-(1-(R)-(3,5-(dimethoxy)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

397) 2-(R)-(1-(R)-(3,5-(dimethoxy)phenyl)ethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

398) 2-(R)-(1-(R)-(3-(fluoro)-5-(trifluoromethyl)phenyl)-ethoxy)-3-(S)-(4-fluorophenyl)-morpholine;

399) 2-(R)-(1-(R)-(3-(fluorophenyl)-5-(trifluoromethyl) ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2, 4-triazolo)methyl)morpholine;

400) 2-(R)-(1-(R)-(3-(fluorophenyl)-5-(trifluoromethyl) ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(1,2,4-triazolo) methyl)-morpholine;

401) 2-(R)-(1-(R)-(3-(fluorophenyl)-5-(trifluoromethyl) ethoxy)-3-(S)-(4-fluorophenyl)-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

402) 2-(R)-(1-(R)-(3-(chloro)-5-(trifluoromethyl)phenyl)-ethoxy)-3-(S)-(4-fluorophenyl)-morpholine;

403) 2-(R)-(1-(R)-(3-(chlorophenyl)-5-(trifluoromethyl) ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2, 4-triazolo)methyl)morpholine;

404) 2-(R)-(1-(R)-(3-(chlorophenyl)-5-(trifluoromethyl) ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo) methyl)-morpholine;

405) 2-(R)-(1-(R)-(3-(chlorophenyl)-5-(trifluoromethyl) ethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

406) 2-(R)-(1-(R)-(3,5-(dimethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;

407) 2-(R)-(1-(R)-(3,5-(dimethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl) morpholine;

408) 2-(R)-(1-(R)-(3,5-(dimethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

409) 2-(R)-(1-(R)-(3,5-(dimethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

410) 2-(R)-(1-(R)-(3-(fluoro)-5-(methyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;

411) 2-(R)-(1-(R)-(3-(fluoro)-5-(methyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo) methyl)morpholine;

412) 2-(R)-(1-(R)-(3-(fluoro)-5-(methyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

413) 2-(R)-(1-(R)-(3-(fluoro)-5-(methyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

414) 2-(R)-(1-(R)-(3-(chloro)-5-(methyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;

415) 2-(R)-(1-(R)-(3-(chloro)-5-(methyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo) methyl)morpholine;

416) 2-(R)-(1-(R)-(3-(chloro)-5-(methyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

417) 2-(R)-(1-(R)-(3-(chloro)-5-(methyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

418) 2-(R)-(1-(R)-(3-(bromo)-5-(methyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;

419) 2-(R)-(1-(R)-(3-(bromo)-5-(methyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo) methyl)morpholine;

420) 2-(R)-(1-(R)-(3-(bromo)-5-(methyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

421) 2-(R)-(1-(R)-(3-(bromo)-5-(methyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

422) 2-(R)-(1-(R)-(3-(isopropoxy)phenyl)ethoxy)-3-(S)-(4-fluoro) phenyl-morpholine;

423) 2-(R)-(1-(R)-(3-(isopropoxy)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl) morpholine;

424) 2-(R)-(1-(R)-(3-(isopropoxy)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

425) 2-(R)-(1-(R)-(3-(isopropoxy)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

426) 2-(R)-(1-(R)-(3-(isopropoxy)-5-(trifluoromethyl) phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;

427) 2-(R)-(1-(R)-(3-(isopropoxy)-5-(trifluoromethyl) phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H, 4H-1,2,4-triazolo)methyl)-morpholine;

428) 2-(R)-(1-(R)-(3-(isopropoxy)-5-(trifluoromethyl) phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

429) 2-(R)-(1-(R)-(3-(isopropoxy)-5-(trifluoromethyl) phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)morpholine;

430) 2-(R)-(1-(R)-(3-(chloro)-5-(isopropoxy)phenyl) ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;

431) 2-(R)-(1-(R)-(3-(chloro)-5-(isopropoxy)phenyl) ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2, 4-triazolo)methyl)morpholine;

432) 2-(R)-(1-(R)-(3-(chloro)-5-(isopropoxy)phenyl) ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo) methyl)-morpholine;

433) 2-(R)-(1-(R)-(3-(chloro)-5-(isopropoxy)phenyl) ethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

434) 2-(R)-(1-(R)-(3-(fluoro)-5-(isopropoxy)phenyl) ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;

435) 2-(R)-(1-(R)-(3-(fluoro)-5-(isopropoxy)phenyl) ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2, 4-triazolo)methyl)morpholine;

436) 2-(R)-(1-(R)-(3-(fluoro)-5-(isopropoxy)phenyl) ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo) methyl)-morpholine;

437) 2-(R)-(1-(R)-(3-(fluoro)-5-(isopropoxy)phenyl) ethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

438) 2-(R)-(1-(R)-(3-(t-butyl)-5-(chloro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;

439) 2-(R)-(1-(R)-(3-(t-butyl)-5-(chloro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo) methyl)morpholine;

440) 2-(R)-(1-(R)-(3-(t-butyl)-5-(chloro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

441) 2-(R)-(1-(R)-(3-(t-butyl)-5-(chloro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

442) 2-(R)-(1-(R)-(3-(t-butyl)-5-(trifluoromethyl)phenyl) ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;

443) 2-(R)-(1-(R)-(3-(t-butyl)-5-(trifluoromethyl)phenyl) ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2, 4-triazolo)methyl)morpholine;

444) 2-(R)-(1-(R)-(3-(t-butyl)-5-(trifluoromethyl)phenyl) ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo) methyl)-morpholine;

445) 2-(R)-(1-(R)-(3-(t-butyl)-5-(trifluoromethyl)phenyl) ethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)morpholine;

446) 2-(R)-(1-(R)-(3,5-(dimethyl)-4-(fluoro)phenyl)ethoxy) -3-(S)-(4-fluoro)phenyl-morpholine;

447) 2-(R)-(1-(R)-(3,5-(dimethyl)-4-(fluoro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine;

448) 2-(R)-(1-(R)-(3,5-(dimethyl)-4-(fluoro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

449) 2-(R)-(1-(R)-(3,5-(dimethyl)-4-(fluoro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

450) 2-(R)-(1-(R)-(3,5-(dimethyl)-4-(chloro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;

451) 2-(R)-(1-(R)-(3,5-(dimethyl)-4-(chloro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine;

452) 2-(R)-(1-(R)-(3,5-(dimethyl)-4-(chloro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

453) 2-(R)-(1-(R)-(3,5-(dimethyl)-4-(chloro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

454) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-4-(fluoro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;

455) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-4-(fluoro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;

456) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-4-(fluoro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

457) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-4-(fluoro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)morpholine;

458) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-4-(chloro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;

459) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-4-(chloro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;

460) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-4-(chloro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

461) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-4-(chloro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)morpholine;

462) 2-(R)-(1-(R)-(3,5-(dichloro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;

463) 2-(R)-(1-(R)-(3,5-(dichloro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine;

464) 2-(R)-(1-(R)-(3,5-(dichloro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

465) 2-(R)-(1-(R)-(3,5-(dichloro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

466) 2-(R)-(1-(R)-(3,5-(difluoro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;

467) 2-(R)-(1-(R)-(3,5-(difluoro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine;

468) 2-(R)-(1-(R)-(3,5-(difluoro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

469) 2-(R)-(1-(R)-(3,5-(difluoro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

470) 2-(R)-(1-(R)-(1-(naphthyl)ethoxy)-3-(S)-(4-fluoro)phenylmorpholine;

471) 2-(R)-(1-(R)-(1-(naphthyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;

472) 2-(R)-(1-(R)-(1-(naphthyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

473) 2-(R)-(1-(R)-(1-(naphthyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

474) 2-(R)-(1-(R)-(1-(4-(fluoro)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;

475) 2-(R)-(1-(R)-(1-(4-(fluoro)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine;

476) 2-(R)-(1-(R)-(1-(4-(fluoro)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

477) 2-(R)-(1-(R)-(1-(4-(fluoro)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

478) 2-(R)-(1-(R)-(1-(3-(fluoro)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;

479) 2-(R)-(1-(R)-(1-(3-(fluoro)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine;

480) 2-(R)-(1-(R)-(1-(3-(fluoro)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

481) 2-(R)-(1-(R)-(1-(3-(fluoro)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

482) 2-(R)-(1-(R)-(1-(3-(chloro)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;

483) 2-(R)-(1-(R)-(1-(3-(chloro)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine;

484) 2-(R)-(1-(R)-(1-(3-(chloro)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

485) 2-(R)-(1-(R)-(1-(3-(chloro)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

486) 2-(R)-(1-(R)-(1-(3-(methyl)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;

487) 2-(R)-(1-(R)-(1-(3-(methyl)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine;

488) 2-(R)-(1-(R)-(1-(3-(methyl)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

489) 2-(R)-(1-(R)-(1-(3-(methyl)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

490) 2-(R)-(1-(R)-(1-(3-(trifluoromethyl)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;

491) 2-(R)-(1-(R)-(1-(3-(trifluoromethyl)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine;

492) 2-(R)-(1-(R)-(1-(3-(trifluoromethyl)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

493) 2-(R)-(1-(R)-(1-(3-(trifluoromethyl)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

494) 2-(R)-(1-(R)-(3-(thiomethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;

495) 2-(R)-(1-(R)-(3-(thiomethylphenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine;

496) 2-(R)-(1-(R)-(3-(thiomethylphenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

497) 2-(R)-(1-(R)-(3-(thiomethylphenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

498) 2-(R)-(1-(R)-(3-(thiomethyl)-5-(trifluoromethyl) phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;

499) 2-(R)-(1-(R)-(3-(thiomethyl-5-(trifluoromethyl) phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H, 4H-1,2,4-triazolo)methyl)-morpholine;

500) 2-(R)-(1-(R)-(3-(thiomethyl-5-(trifluoromethyl) phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

501) 2-(R)-(1-(R)-(3-(thiomethyl-5-(trifluoromethyl) phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)morpholine;

502) 2-(R)-(1-(R)-(2,2-(dimethyl)-5-(thiomethyl)-2,3-dihydrobenzofuran-7-yl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;

503) 2-(R)-(1-(R)-(2,2-(dimethyl)-5-(thiomethyl)-2,3-dihydrobenzofuran-7-yl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;

504) 2-(R)-(1-(R)-(2,2-(dimethyl)-5-(thiomethyl)-2,3-dihydrobenzofuran-7-yl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

505) 2-(R)-(1-(R)-(2,2-(dimethyl)-5-(thiomethyl)-2,3-dihydrobenzofuran-7-yl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

506) 2-(R)-(1-(R)-(3,5-(dimethoxy)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;

507) 2-(R)-(1-(R)-(3,5-(dimethoxy)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo) methyl)morpholine;

508) 2-(R)-(1-(R)-(3,5-(dimethoxy)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

509) 2-(R)-(1-(R)-(3,5-(dimethoxy)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

510) 2-(R)-(1-(R)-(phenyl)ethoxy)-3-(S)-phenyl-morpholine;

511) 2-(R)-(1-(R)-(phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;

512) 2-(R)-(1-(R)-(phenyl)ethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

513) 2-(R)-(1-(R)-(phenyl)ethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

514) 2-(R)-(1-(R)-(phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl morpholine;

515) 2-(R)-(1-(R)-(phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;

516) 2-(R)-(1-(R)-(phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

517) 2-(R)-(1-(R)-(phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

518) 2-(R)-(1-(R)-(3-(fluoro)phenyl)ethoxy)-3-(S)-phenyl-morpholine;

519) 2-(R)-(1-(R)-(3-(fluoro)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;

520) 2-(R)-(1-(R)-(3-(fluoro)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

521) 2-(R)-(1-(R)-(3-(fluoro)phenyl)ethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

522) 2-(R)-(1-(R)-(3-(fluoro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenylmorpholine;

523) 2-(R)-(1-(R)-(3-(fluoro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl) -morpholine;

524) 2-(R)-(1-(R)-(3-(fluoro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

525) 2-(R)-(1-(R)-(3-(fluoro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

526) 2-(R)-(1-(R)-(4-(fluoro)phenyl)ethoxy)-3-(S)-phenyl-morpholine;

527) 2-(R)-(1-(R)-(4-(fluoro)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;

528) 2-(R)-(1-(R)-(4-(fluoro)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

529) 2-(R)-(1-(R)-(4-(fluoro)phenyl)ethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

530) 2-(R)-(1-(R)-(4-(fluoro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenylmorpholine;

531) 2-(R)-(1-(R)-(4-(fluoro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl) -morpholine;

532) 2-(R)-(1-(R)-(4-(fluoro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

533) 2-(R)-(1-(R)-(4-(fluoro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

534) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(3-fluoro)phenyl-morpholine;

535) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(3-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine;

536) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(3-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

537) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(3-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo) methyl)-morpholine;

538) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(3,4-difluoro)phenyl-morpholine;

539) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(3,4-difluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine;

540) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(3,4-difluoro)phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

541) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(3,4-difluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo) methyl)-morpholine;

542) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(3,4-dichloro)phenyl-morpholine;

543) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(3,4-dichloro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine;

544) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(3,4-dichloro)phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

545) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(3,4-dichloro)phenyl-4-(4-(2-oxo-1,3-imidazolo) methyl)-morpholine;

546) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(3,4-dimethyl)phenyl-morpholine;

547) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(3,4-dimethyl)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine;

548) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(3,4-dimethyl)phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

549) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(3,4-dimethyl)phenyl-4-(4-(2-oxo-1,3-imidazolo) methyl)-morpholine;

550) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-3,4-methylenedioxyphenyl-morpholine;

551) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-3,4-methylenedioxyphenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine;

552) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-3,4-methylenedioxyphenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

553) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-3,4-methylenedioxyphenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)morpholine;

554) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(2-naphthyl)-morpholine;

555) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(2-naphthyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine;

556) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(2-naphthyl)-4-(3-(1,2,4-triazolo)methyl)-morpholine;

557) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(2-naphthyl)-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

558) 2-(R)-(1-(R)-(3-(fluorophenyl)-5-(trifluoromethyl)ethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

559) 2-(R)-(1-(R)-(3-(fluorophenyl)-5-(trifluoromethyl)ethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

560) 2-(R)-(1-(R)-(3-(chlorophenyl)-5-(trifluoromethyl)ethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

561) 2-(R)-(1-(R)-(3-(chlorophenyl)-5-(trifluoromethyl)ethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

562) 2-(R)-(1-(R)-(3,5-(dimethyl)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

563) 2-(R)-(1-(R)-(3,5-(dimethyl)phenyl)ethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

564) 2-(R)-(1-(R)-(3-(fluoro)-5-(methyl)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

565) 2-(R)-(1-(R)-(3-(fluoro)-5-(methyl)phenyl)ethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

566) 2-(R)-(1-(R)-(3-(chloro)-5-(methyl)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(-1H,4H-1,2,4-triazolo)methyl)-morpholine;

567) 2-(R)-(1-(R)-(3-(chloro)-5-(methyl)phenyl)ethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

568) 2-(R)-(1-(R)-(3-(bromo)-5-(methyl)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

569) 2-(R)-(1-(R)-(3-(bromo)-5-(methyl)phenyl)ethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

570) 2-(R)-(1-(R)-(3-(isopropoxy)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

571) 2-(R)-(1-(R)-(3-(isopropoxy)phenyl)ethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

572) 2-(R)-(1-(R)-(3-(isopropoxy)-5-(trifluoromethyl)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(-1H,4H-1,2,4-triazolo)methyl)-morpholine;

573) 2-(R)-(1-(R)-(3-(isopropoxy)-5-(trifluoromethyl)phenyl)ethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

574) 2-(R)-(1-(R)-(3-(chloro)-5-(isopropoxy)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(-1H,4H-1,2,4-triazolo)methyl)-morpholine;

575) 2-(R)-(1-(R)-(3-(chloro)-5-(isopropoxy)phenyl)ethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

576) 2-(R)-(1-(R)-(3-(fluoro)-5-(isopropoxy)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(-1H,4H-1,2,4-triazolo)methyl)-morpholine;

577) 2-(R)-(1-(R)-(3-(fluoro)-5-(isopropoxy)phenyl)ethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

578) 2-(R)-(1-(R)-(3-(t-butyl)-5-(chloro)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(-1H,4H-1,2,4-triazolo)methyl)-morpholine;

579) 2-(R)-(1-(R)-(3-(t-butyl)-5-(chloro)phenyl)ethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

580) 2-(R)-(1-(R)-(3-(t-butyl)-5-(trifluoromethyl)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(-1H,4H-1,2,4-triazolo)methyl)-morpholine;

581) 2-(R)-(1-(R)-(3-(t-butyl)-5-(trifluoromethyl)phenyl)ethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

582) 2-(R)-(1-(R)-(3,5-(dimethyl)-4-(fluoro)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

583) 2-(R)-(1-(R)-(3,5-(dimethyl)-4-(fluoro)phenyl)ethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

584) 2-(R)-(1-(R)-(3,5-(dimethyl)-4-(chloro)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(-1H,4H-1,2,4-triazolo)methyl)-morpholine;

585) 2-(R)-(1-(R)-(3,5-(dimethyl)-4-(chloro)phenyl)ethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

586) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-4-(fluoro)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(-1H,4H-1,2,4-triazolo)methyl)-morpholine;

587) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-4-(fluoro)phenyl)ethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

588) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-4-(chloro)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(-1H,4H-1,2,4-triazolo)methyl)-morpholine;

589) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-4-(chloro)phenyl)ethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

590) 2-(R)-(1-(R)-(3,5-(dichloro)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(-1H,4H-1,2,4-triazolo)methyl)-morpholine;

591) 2-(R)-(1-(R)-(3,5-(dichloro)phenyl)ethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

592) 2-(R)-(1-(R)-(3,5-(difluoro)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

593) 2-(R)-(1-(R)-(3,5-(difluoro)phenyl)ethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

594) 2-(R)-(1-(R)-(1-(naphthyl)ethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

595) 2-(R)-(1-(R)-(1-(naphthyl)ethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

596) 2-(R)-(1-(R)-(1-(4-(fluoro)naphthyl))ethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

597) 2-(R)-(1-(R)-(1-(4-(fluoro)naphthyl))ethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

598) 2-(R)-(1-(R)-(1-(3-(fluoro)naphthyl))ethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

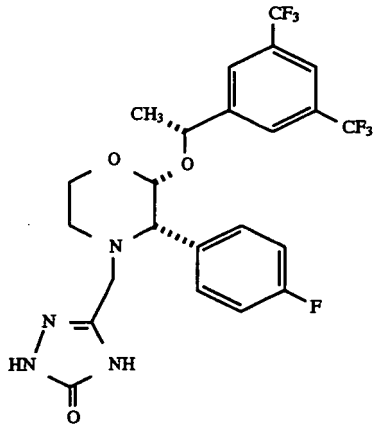
599) 2-(R)-(1-(R)-(1-(3-(fluoro)naphthyl))ethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

600) 2-(R)-(1-(R)-(1-(3-(chloro)naphthyl))ethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

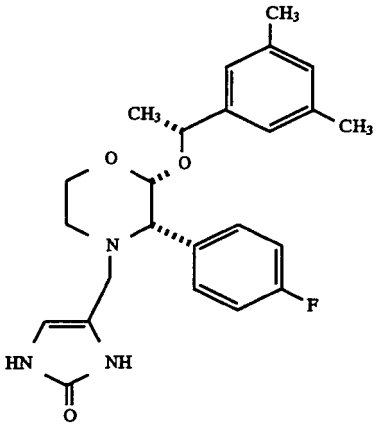
601) 2-(R)-(1-(R)-(1-(3-(chloro)naphthyl))ethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;

and pharmaceutically acceptable salts thereof.

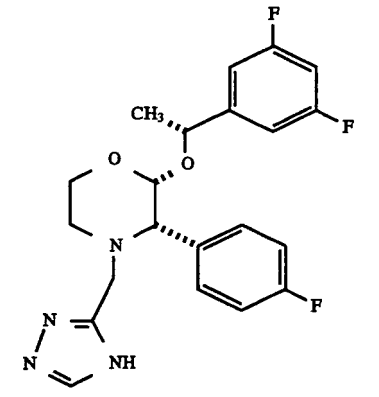
Representative examples of the nomenclature employed herein are given below:



96) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl) ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl-morpholine;



449) 2-(R)-(1-(R)-(3,5-(dimethyl)-4-(fluoro)phenyl) ethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl)-morpholine;



468) 2-(R)-(1-(R)-(3,5-(difluoro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine.

Specific compounds within the scope of the present invention include:

(1) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine N-oxide;

(2) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(4-monophosphoryl-5-oxo-1H,-1,2,4-triazolo)methyl)morpholine;

(3) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(1-monophosphoryl-5-oxo-1H,-1,2,4-triazolo)methyl)morpholine;

(4) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(2-monophosphoryl-5-oxo-1H,-1,2,4-triazolo)methyl)morpholine;

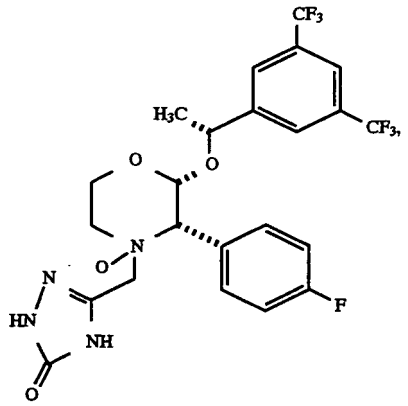
(5) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(5-oxyphosphoryl-1H,-1,2,4-triazolo)methyl)morpholine;

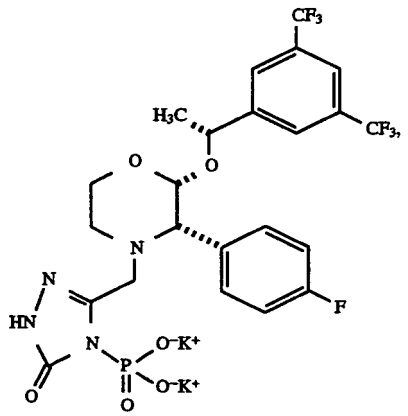
(6) 2-(S)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(1-phosphoryl-5-oxo-4H-1,2,4-triazolo)methyl)morpholine;

or a pharmaceutically acceptable salt thereof.

Particularly prefered compounds include those wherein the pharmaceutically acceptable salt is the bis(N-methyl-D-glucamine) salt.

Specific compounds within the scope of the present invention also include:





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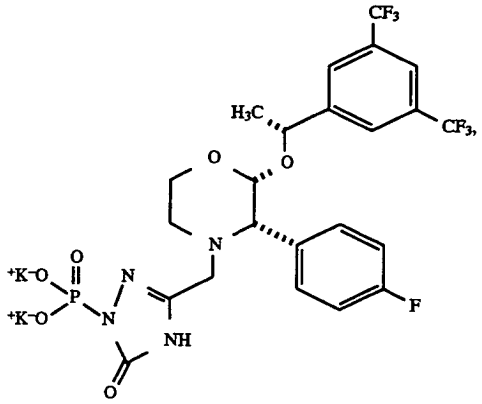

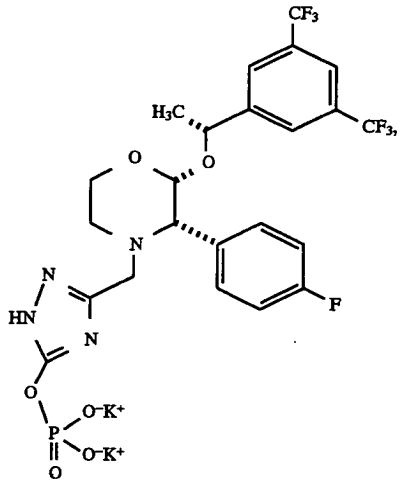

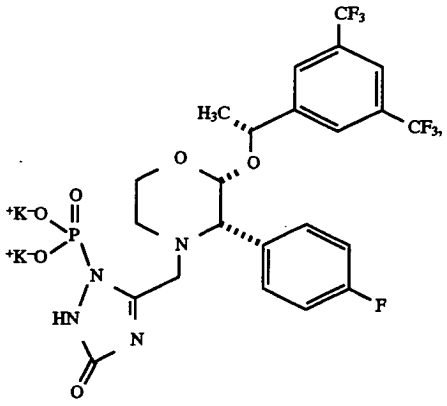

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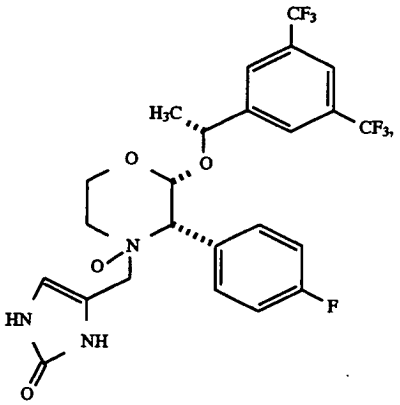

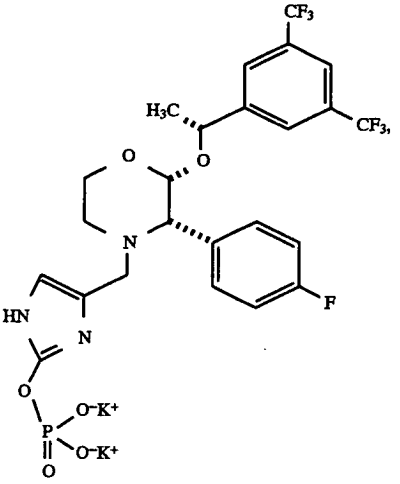

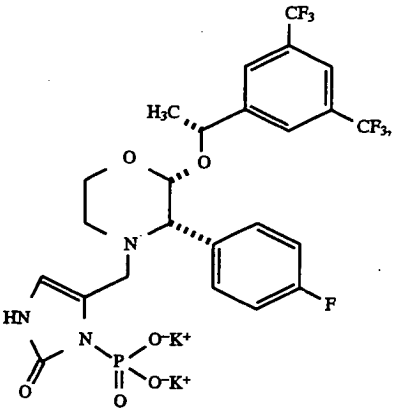

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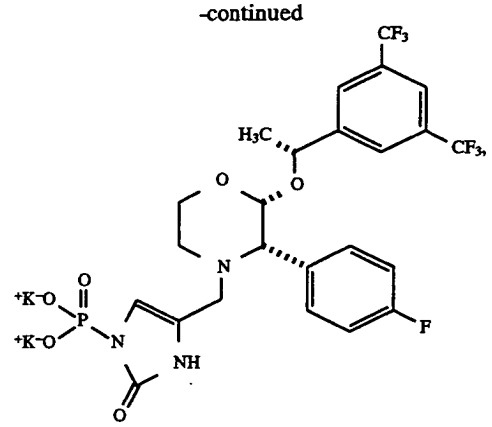


wherein K^+ is a pharmaceutically acceptable counterion.

A particularly preferred compound within the scope of the present invention is 2-(R)-(1-(R)-(3,5-bis(trifluoro-methyl) phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1-phosphoryl-5-oxo-4H-1,2,4-triazolo)methylmorpholine, or a pharmaceutically acceptable salt thereof, and a specific particularly preferred compound within the scope of the present invention is 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy) -3-(S)-(4-fluoro)phenyl-4-(3-(1-phosphoryl-5-oxo-4H-1,2, 4-triazolo)methylmorpholine, bis(N-methyl-D-glucamine).

TACHYKININ ANTAGONISM ASSAY

The compounds of this invention are useful for antagonizing tachykinins, in particular substance P and neurokinin A in the treatment of gastrointestinal disorders, central nervous system disorders, inflammatory diseases, pain or migraine and asthma in a mammal in need of such treatment. This activity can be demonstrated by the following assay.

A. Receptor Expression in COS

To express the cloned human neurokinin-1 receptor (NK1R) transiently in COS, the cDNA for the human NK1R was cloned into the expression vector pCDM9 which was derived from pCDM8 (INVITROGEN) by inserting the ampicillin resistance gene (nucleotide 1973 to 2964 from BLUESCRIPT SK+) into the Sac II site. Transfection of 20 ug of the plasmid DNA into 10 million COS cells was achieved by electroporation in 800 ul of transfection buffer (135 mM NaCl, 1.2 mM $CaCl_2$, 1.2 mM $MgCl_2$, 2.4 mM K_2HPO_4, 0.6 mM KH_2PO_4, 10 mM glucose, 10 mM HEPES pH 7.4) at 260 V and 950 uF using the IBI GENEZAPPER (IBI, New Haven, Conn.). The cells were incubated in 10% fetal calf serum, 2 mM glutamine, 100 U/ml penicillin-streptomycin, and 90% DMEM media (GIBCO, Grand Island, N.Y.) in 5% CO_2 at 37° C. for three days before the binding assay.

B. Stable Expression in CHO

To establish a stable cell line expressing the cloned human NK1R, the cDNA was subcloned into the vector pRcCMV (INVITROGEN). Transfection of 20 ug of the plasmid DNA into CHO cells was achieved by electroporation in 800 ul of transfection buffer suplemented with 0.625 mg/ml Herring sperm DNA at 300 V and 950 uF using the IBI GENEZAPPER (IBI). The transfected cells were incubated in CHO media [10% fetal calf serum, 100 U/ml pennicilin-streptomycin, 2 mM glutamine, 1/500 hypoxanthine-thymidine (ATCC), 90% IMDM media (JRH BIOSCIENCES, Lenexa, Kans.), 0.7 mg/ml G418 (GIBCO)] in 5% CO_2 at 37° C. until colonies were visible. Each colony was separated and propagated. The cell clone with the highest number of human NK1R was selected for subsequent applications such as drug screening.

C. Assay Protocol using COS or CHO

The binding assay of human NK1R expressed in either COS or CHO cells is based on the use of ^{125}I-substance P (^{125}I-SP, from DU PONT, Boston, Mass.) as a radioactively labeled ligand which competes with unlabeled substance P or any other ligand for binding to the human NK1R. Monolayer cell cultures of COS or CHO were dissociated by the non-enzymatic solution (SPECIALTY MEDIA, Lavallette, N.J.) and resuspended in appropriate volume of the binding buffer (50 mM Tris pH 7.5, 5 mM $MnCl_2$, 150 mM NaCl, 0.04 mg/ml bacitracin, 0.004 mg/ml leupeptin, 0.2 mg/ml BSA, 0.01 mM phosphoramidon) such that 200 ul of the cell suspension would give rise to about 10,000 cpm of specific ^{125}I-SP binding (approximately 50,000 to 200, 000 cells). In the binding assay, 200 ul of cells were added to a tube containing 20 ul of 1.5 to 2.5 nM of ^{125}I-SP and 20 ul of unlabeled substance P or any other test compound. The tubes were incubated at 4° C. or at room temperature for 1 hour with gentle shaking. The bound radioactivity was separated from unbound radioactivity by GF/C filter (BRANDEL, Gaithersburg, Md.) which was pre-wetted with 0.1% polyethylenimine. The filter was washed with 3 ml of wash buffer (50 mM Tris pH 7.5, 5 mM $MnCl_2$, 150 mM NaCl) three times and its radioactivity was determined by gamma counter.

The activation of phospholipase C by NK1R may also be measured in CHO cells expressing the human NK1R by determining the accumulation of inositol monophosphate which is a degradation product of IP_3. CHO cells are seeded in 12-well plate at 250,000 cells per well. After incubating in CHO media for 4 days, cells are loaded with 0.025 uCi/ml of ^{3}H-myoinositol by overnight incubation. The extracellular radioactivity is removed by washing with phosphate buffered saline. LiCl is added to the well at final concentration of 0.1 mM with or without the test compound, and incubation is continued at 37° C. for 15 min. Substance P is added to the well at final concentration of 0.3 nM to activate the human NK1R. After 30 min of incubation at 37° C., the media is removed and 0.1N HCl is added. Each well is sonicated at 4° C. and extracted with $CHCl_3$/methanol (1:1). The aqueous phase is applied to a 1 ml Dowex AG 1×8 ion exchange column. The column is washed with 0.1N formic acid followed by 0.025M ammonium formate-0.1N formic acid. The inositol monophosphate is eluted with 0.2M ammonium formate-0.1N formic acid and quantitated by beta counter.

The compounds of Formula I as exemplified in the Examples below have been found to displace radioactive ligand for the neurokinin-1 receptor at a concentration range of 0.01 nM to 1.0 μM.

The activity of the present compounds may also be demonstrated by the assay disclosed by Lei, et al., *British J. Pharmacol.*, 105, 261–262 (1992).

The compounds of the present invention are useful in the prevention and treatment of a wide variety of clinical conditions which are characterized by the presence of an excess of tachykinin, in particular substance P, activity. These conditions may include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; epilepsy; neurodegenerative disorders such as dementia, including senile dementia of the Alzheimer type, Alzheimer's disease and Down's syndrome; demyelinating diseases such as multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease) and other neuropathological disorders such as peripheral neuropathy, for example AIDS related neuropathy, diabetic neuropathy, chemotherapy-induced neuropathy, and postherpetic and other neuralgias; small cell carcinomas such as

small cell lung cancer; respiratory diseases, particularly those associated with excess mucus secretion, such as chronic obstructive airways disease, bronchopneumonia, chronic bronchitis, acute bronchitis, diffuse panbronchilitis, emphysema, cystic fibrosis, asthma, and bronchospasm; airways disease modulated by neurogenic inflammation; laryngopharhngitis; bronchiectasis; conoisis; whooping cough; pulmonary tuberculosis; diseases associated with decreased glandular secretions, including lacrimation, such as Sjogren's syndrome, hyperlipoproteinemias IV and V, hemochromatosis, sarcoidosis, or amyloidosis; iritis; inflammatory diseases such as inflammatory bowel disease, inflammatory intestinal disease, psoriasis, fibrositis, ocular intimation, osteoarthritis, rheumatoid arthritis, pruritis, and sunburn; hepatitis; allergies such as eczema and rhinitis; hypersensitivity disorders such as poison ivy; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, dry eye syndrome, and the like; ophthalmic conditions associated with cell proliferation such as proliferative vitreoretinopathy; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis; hemodialysis-associated itching; lichen planus; oedema, such as oedema caused by thermal injury; addiction disorders such as alcoholism; mental disease, particularly anxiety and depression; stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; dysthymic disorders; tenalgia attended to hypedipidemia; post-operative neuroma, particularly of mastectomy; vulvar vestibulitis; amniogenesis; adverse immunological reactions such as rejection of transplanted tissues and disorders related to immune enhancement or suppression, such as systemic lupus erythmatosus; gastrointestinal (GI) disorders, including inflammatory disorders, and diseases of the GI tract, such as gastritis, gastroduodenal ulcers, gastric carcinomas, gastric lymphomas, disorders associated with the neuronal control of viscera such as ulcerative colitis, Crohn's disease, irritable bowel syndrome, nausea, and emesis, including acute, delayed, post-operative, late-phase, and anticipatory emesis, such as emesis or nausea induced by for example chemotherapy, radiation, surgery, migraine, toxins, such as metabolic or microbial toxins, viral or bacterial infections, pregnancy, vestibular disorder, motion, mechanical stimulation, gastrointestinal obstruction, reduced gastrointestinal motility, visceral pain, psychological stress or disturbance, high altitude, weightlessness, opioid analgesics, intoxication, resulting for example from consumption of alcohol, and variations in intercranial pressure, in particular, for example, drug or radiation induced emesis or post-operative nausea and vomiting; disorders of bladder function such as cystitis, bladder detrusor hyperreflexia, and incontinence; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders of blood flow caused by vasodilation and vasospastic diseases such as angina, migraine and Reynaud's disease; and pain or nociception, for example, chronic pain or that attributable to or associated with any of the foregoing conditions especially the transmission of pain in migraine, or such as headache, toothache, cancerous pain, back pain, and superficial pain on congelation, burn, herpes zoster or diabetic neuropathy. Hence, these compounds may be readily adapted to therapeutic use for the treatment of physiological disorders associated with an excessive stimulation of tachykinin receptors, especially neurokinin-1, and as neurokinin-1 antagonists in the control and/or treatment of any of the aforesaid clinical conditions in mammals, including humans.

The compounds of the present invention are also of value in the treatment of a combination of the above conditions, in particular in the treatment of combined post-operative pain and post-operative nausea and vomiting.

The compounds of the present invention are particularly useful in the treatment of nausea or emesis, including acute, delayed, post-operative, late-phase, and anticipatory emesis, such as emesis or nausea induced by for example chemotherapy, radiation, surgery, migraine, toxins, such as metabolic or microbial toxins, viral or bacterial infections, pregnancy, vestibular disorder, motion, mechanical stimulation, gastrointestinal obstruction, reduced gastrointestinal motility, visceral pain, psychological stress or disturbance, high altitude, weightlessness, opioid analgesics, intoxication, resulting for example from consumption of alcohol, and variations in intercranial pressure. Most especially, this compound is of use in the treatment of emesis induced by antineoplastic (cytotoxic) agents including those routinely used in cancer chemotherapy.

Examples of such chemotherapeutic agents include alkylating agents, for example, nitrogen mustards, ethyleneimine compounds, alkyl sulfonates and other compounds with an alkylating action such as nitrosoureas, cisplatin, and dacarbazine; antimetabolites, for example, folic acid, purine or pyrimidine antagonists; mitotic inhibitors, for example, vinca alkaloids and derivatives of podophyllotoxin; and cytotoxic antibiotics.

Particular examples of chemotherapeutic agents are described, for example, by D. J. Stewart in "Nausea and Vomiting: Recent Research and Clinical Advances", Eds. J. Kucharczyk, et al., CRC Press Inc., Boca Raton, Fla., U.S.A. (1991), pages 177–203, especially page 188. Commonly used chemotherapeutic agents include cisplatin, dacarbazine (DTIC), dactinomycin, mechlorethamine (nitrogen mustard), streptozocin, cyclophosphamide, carmustine (BCNU), lomustine (CCNU), doxorubicin (adriamycin), daunorubicin, procarbazine, mitomycin, cytarabine, etoposide, methotrexate, 5-fluorouracil, vinblastine, vincristine, bleomycin, and chlorambucil [R. J. Gralla, et al., *Cancer Treatment Reports*, 68(1), 163–172 (1984)].

The compounds of the present invention are also of use in the treatment of emesis induced by radiation including radiation therapy such as in the treatment of cancer, or radiation sickness, and in the treatment of post-operative nausea and vomiting.

The compounds of the present invention are also of use in the prevention or treatment of disorders of the central nervous system such as anxiety, psychosis and schizophrenia; neurodegenerative disorders such as senile dementia of the Alzheimer type, Alzheimer's disease and Down's syndrome; respiratory diseases, particularly those associated with excess mucus secretion, such as chronic obstructive airways disease, broncho-pneumonia, chronic bronchitis, cystic fibrosis and asthma, and bronchospasm; inflammatory diseases such as inflammatory bowel disease, osteoarthritis and rheumatoid arthritis; adverse immunological reactions such as rejection of transplanted tissues; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the neuronal control of viscera such as ulcerative colitis, Crohn's disease and incontinence; disorders of blood flow caused by vasodilation; and pain or nociception, for example, that attributable to or associated with any of the foregoing conditions or the transmission of pain in migraine (both prophylaxis and acute treatment).

As calcium channel blocking agents some of the compounds of the present invention are useful in the prevention of treatment of clinical conditions which benefit from inhibition of the transfer of calcium ions across the plasma membrane of cells. These include diseases and disorders of

the heart and vascular system such as angina pectoris, myocardial infarction, cardiac arrhythmia, cardiac hypertrophy, cardiac vasospasm, hypertension, cerebrovascular spasm and other ischemic disease. Furthermore, these compounds may be capable of lowering elevated intraocular pressure when administered topically to the hypertensive eye in solution in a suitable ophthalmic vehicle. Also, these compounds may be useful in the reversal of multidrug resistance in tumor cells by enhancing the efficacy of chemotherapeutic agents. In addition, these compounds may have activity in blocking calcium channels in insect brain membranes and so may be useful as insecticides.

The compounds of the present invention are particularly useful in the treatment of pain or nociception and/or inflammation and disorders associated therewith such as, for example: neuropathy, such as diabetic or peripheral neuropathy and chemotherapy-induced neruopathy; postherpetic and other neuralgias; asthma; osteoarthritis; rheumatoid arthritis; and especially migraine. The compounds of the present invention are also particularly useful in the treatment of diseases characterized by neurogenic mucus secretion, especially cystic fibrosis.

For the treatment of certain conditions it may be desirable to employ a compound of the present invention in conjunction with another pharmacologically active agent. For example, a compound of the present invention may be presented together with another therapeutic agent as a combined preparation for simultaneous, separate, or sequential use for the relief of emesis. Such combined preparations may be, for example, in the form of a twin pack. A preferred combination comprises a compound of the present invention with a chemotherapeutic agent such as an alkylating agent, antimetabolite, mitotic inhibitor, or cytotoxic antibiotic, as described above. In general, the currently available dosage forms of the known therapeutic agents for use in such combinations will be suitable.

Similarly, for the treatment of respiratory diseases, such as asthma, a compound of the present invention may be used in conjunction with a bronchodilator, such as a β_2-adrenergic receptor agonist or a tachykinin antagonist which acts at neurokinin-2 receptors. Suitable β_2-adrenergic receptor agonist include: Bambuterol (U.S. Pat. No. 4,419,364 issued to Draco on Dec. 6 , 1983); Bitolterol mesylate (U.S. Pat. No. 4,138,581 issued to Sterling Feb. 6, 1979); Brosaterol (U.S. Pat. No. 4,276,299 issued to Zambon Jun. 30, 1981 and U.S. Pat. No. 4,520,200 issued to Zambon May 28, 1985); Carbuterol (U.S. Pat. No. 3,763,232 issued to Smith Kline Oct. 2, 1973); Clenbuterol (U.S. Pat. No. 3,536,712 issued to Boehringer Ingelheim Oct. 27, 1970); Cimaterol (U.S. Pat. No. 4,407,819 issued to American Cyanamid Oct. 4, 1983); Docarpamine (U.S. Pat. No. 4,228,183 issued to Tanabe Oct. 14, 1980); Dopexamine (U.S. Pat. No. 4,645, 768 issued to Fisons Feb. 24, 1987); Formoterol (U.S. Pat. No. 3,994,974 issued to Yamanouchi Nov. 30, 1976); Mabuterol (U.S. Pat. No. 4,119,710 issued to Boehringer Ingelheim Oct. 10, 1978); Pirbuterol hydrochloride (U.S. 3,700,681 issued to Pfizer Oct. 24, 1972); Procaterol hydrochloride (U.S. Pat. No. 4,026,897 issued to Otsuka May 31, 1977); Ritodrine hydrochloride (U.S. Pat. No. 3,410,944 issued to North American Philips Nov. 12, 1968); or Salmeterol (U.S. Pat. No. 4,992,474 issued to Glaxo Feb. 21, 1991 and U.S. Pat. No. 5,091,422 issued to Glaxo Feb. 25, 1992).

Also, for the treatment of conditions that require antagonism of both neurokinin-1 and neurokinin-2, including disorders associated with bronchoconstriction and/or plasma extravasation in airways, such as asthma, chronic bronchitis, airways disease, or cystic fibrosis; neuropathy, such as diabetic or peripheral neuropathy and chemotherapy-induced neuropathy; osteoarthritis; rheumatoid arthritis; and migraine, a compound of the present invention may be used in conjunction with a tachykinin antagonist which acts at neurokinin-2 receptors, or with tachykinin receptor antagonist which acts at both neurokinin-1 and neurokinin-2 receptors.

Likewise, a compound of the present invention may be employed with a leucotriene antagonist, such a leucotriene D_4 antagonist, exemplfied by those disclosed in Patent Pub. EP O,480,717, published Apr. 15, 1992; Patent Pub. EP O 604,114, published June 1994; U.S. Pat. No. 5,270,324, issued Dec. 14, 1993; and U.S. Pat. No. 4,859,692, issued Aug. 22, 1989. This combination is particularly useful in the treatment of respiratory diseases such as asthma, chronic bronchitis and cough.

A compound of the present invention further may be used in combination with a corticosteroid such as Dexamethasone, Kenalog, Aristocort, Nasalide, Preferid, Benecorten or others such as disclosed in U.S. Pat. Nos. 2,789,118, 2,990,401, 3,048,581, 3,126,375, 3,929,768, 3,996,359, 3,928,326 and 3,749,712.

Similarly, for the prevention or treatment of emesis a compound of the present invention may be used in conjunction with other anti-emetic agents, especially $5HT_3$ receptor antagonists, such as ondansetron, granisetron, tropisetron, decadron, and zatisetron, or $GABA_B$ receptor agonists, such as baclofen. Likewise, for the prevention or treatment of migraine a compound of the present invention may be used in conjunction with other anti-migraine agents, such as ergotamines or $5HT_1$ agonists, especially sumatriptan.

Likewise, for the treatment of behavioral hyperalgesia, a compound of the present invention may be used in conjunction with an antagonist of N-methyl D-aspartate (NMDA), such as dizocilpine. For the prevention or treatment of inflammatory conditions in the lower urinary tract, especially cystitis, a compound of the present invention may be used in conjunction with an antiinflammatory agent, such as a bradykinin receptor antagonist. The compound of the present invention and the other pharmacologically active agent may be administered to a patient simultaneously, sequentially or in combination.

In the treatment of the clinical conditions noted above, the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for oral administration, suppositories for rectal administration, sterile solutions or suspensions for parenteral or intramuscular administration, and the like.

The pharmaceutical compositions of this invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains one or more of the compounds of the present invention, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external, enteral or parenteral applications. The active ingredient may be compounded, for example, with the usual non- toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. The carriers which can be used are water, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form, and in addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. The active object compound is included in the

pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of the disease.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformnlation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solution, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone or gelatin.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening, flavoring and coloring agents, may also be present.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

For the treatment of the clinical conditions and diseases noted above, the compounds of this invention may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques.

The compounds of this invention may be administered to patients (animals and human) in need of such treatment in dosages that will provide optimal pharmaceutical efficacy. The dose will vary from patient to patient depending upon the nature and severity of disease, the patient's weight, special diets then being followed by a patient, concurrent medication, and other factors which those skilled in the art will recognize.

In the treatment of a condition associated with an excess of tachykinins, an appropriate dosage level will generally be about 0.001 to 50 mg per kg patient body weight per day which may be administered in single or multiple doses. Preferably, the dosage level will be about 0.01 to about 25 mg/kg per day; more preferably about 0.05 to about 10 mg/kg per day. For example, in the treatment of conditions involving the neurotransmission of pain sensations, a suitable dosage level is about 0.001 to 25 mg/kg per day, preferably about 0.05 to 10 mg/kg per day, and especially about 0.1 to 5 mg/kg per day. A compound may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day. In the treatment of emesis using an injectableformulation, a suitable dosage level is about 0.001 to 10 mg/kg per day, preferably about 0.005 to 5 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. A compound may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

Several methods for preparing the compounds of this invention are illustrated in the following Schemes and Examples wherein wherein R^2, R^3, R^6, R^7, R^8, R^{11}, R^{12}, R^{13}, A, B, p, Y and Z are as defined above.

TABLE 1

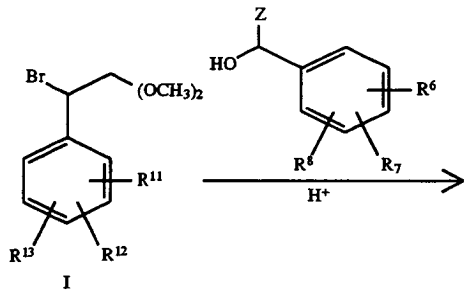
ABBREVIATIONS USED IN SCHEMES AND EXAMPLES

Reagents:	
Et_3N	triethylamine
Ph_3P	triphenylphosphine
TFA	trifluoroacetic acid
NaOEt	sodium ethoxide
DCC	N,N'-dicyclohexylcarbodiimide
DCU	N,N'-dicyclohexylurea
CDI	1,1'-carbonyldiimidazole
MCPBA	m-chloroperbenzoic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
Cbz—Cl	benzyl chloroformate
ACE—Cl	alpha-chloroethyl chloroformate
iPr_2NEt or DIEA	N,N-diisopropylethylamine
NHS	N-hydroxysuccinimide
DIBAL	diisobutylaluminum hydride
Me_2SO_4	dimethyl sulfate
HOBt	1-hydroxybenzotriazole hydrate
EDAC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
Solvents:	
DMF	dimethylformamide
THF	tetrahydrofuran
MeOH	methanol
EtOH	ethanol
AmOH	n-amyl alcohol
AcOH	acetic acid
MeCN	acetonitrile

TABLE 1-continued

ABBREVIATIONS USED IN SCHEMES AND EXAMPLES	
DMSO	dimethylsulfoxide
Others:	
Ph	phenyl
Ar	aryl
Me	methyl
Et	ethyl
iPr	isopropyl
Am	n-amyl
Cbz	carbobenzyloxy (benzyloxy-carbonyl)
BOC	tert-butoxycarbonyl
PTC	phase transfer catalyst
cat.	catalytic
FAB-MS	fast atom bombardment mass spectrometry
rt	room temperature
LG	leaving group (Cl, Br, I, OTs, OMs, OTf, etc.)

SCHEME 1



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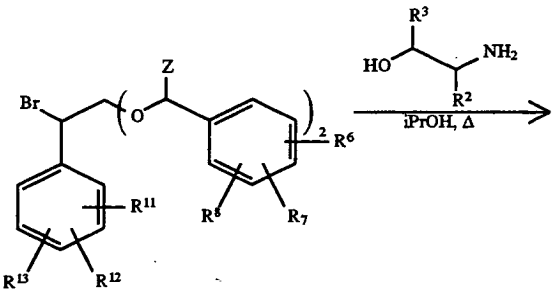

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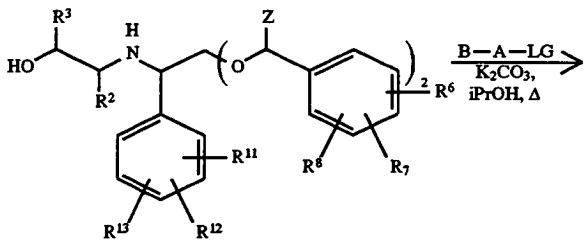

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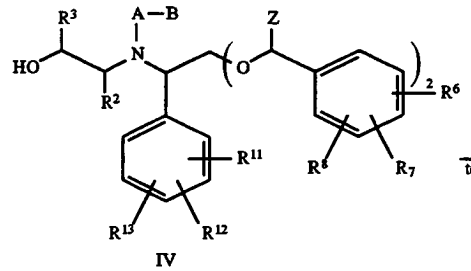
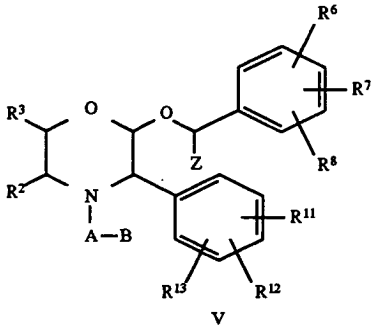


IV

-continued

SCHEME 1



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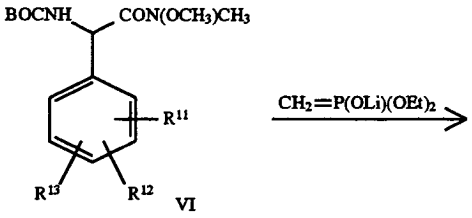
SCHEME 2



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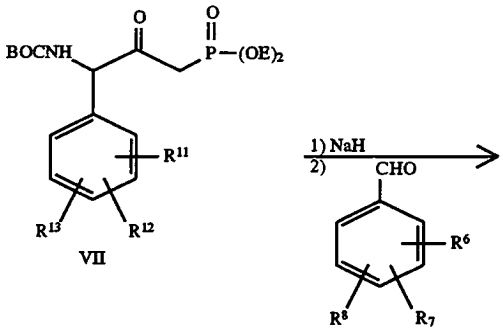

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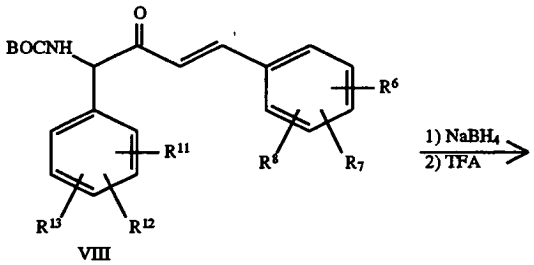

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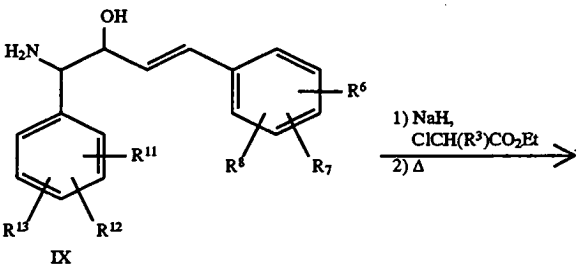

IX

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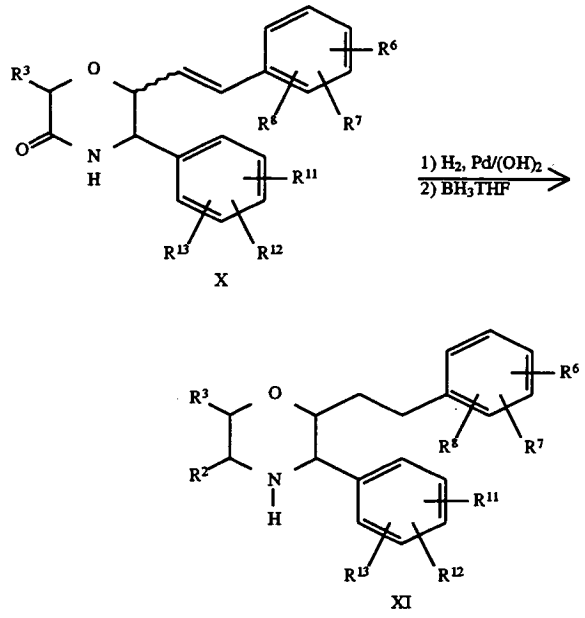
SCHEME 2



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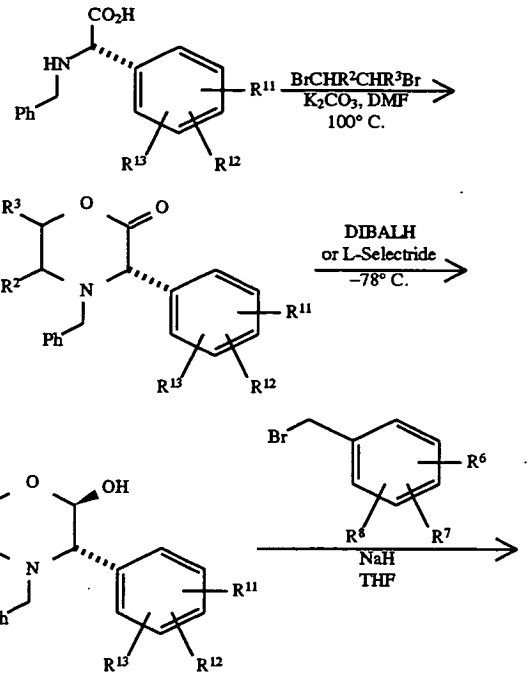
SCHEME 4



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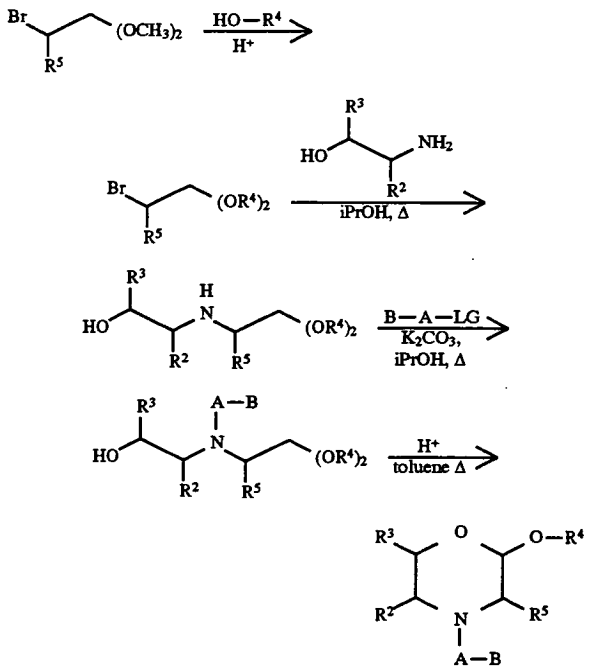

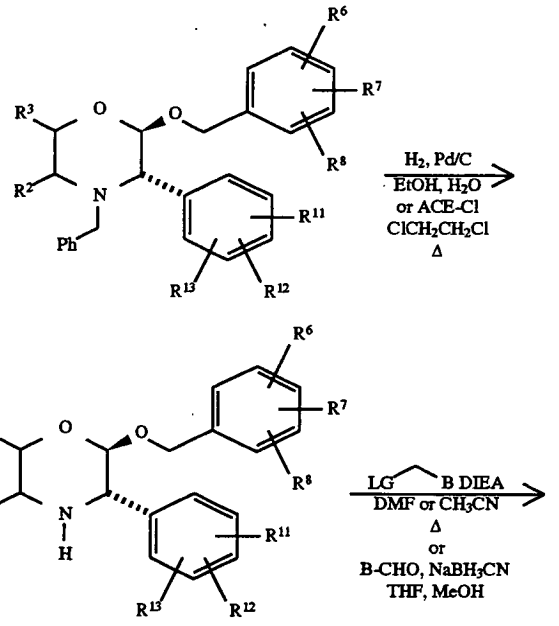

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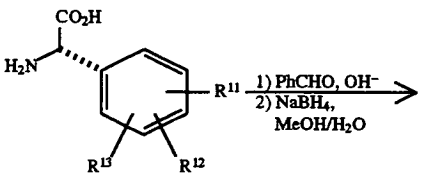
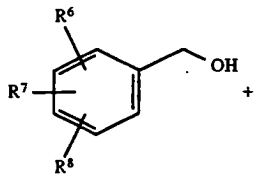
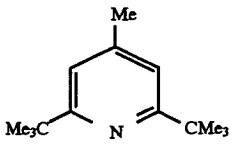
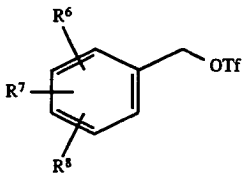


SCHEME 5

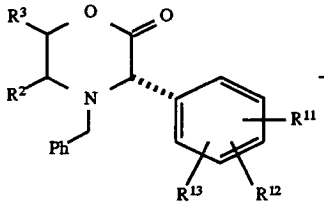




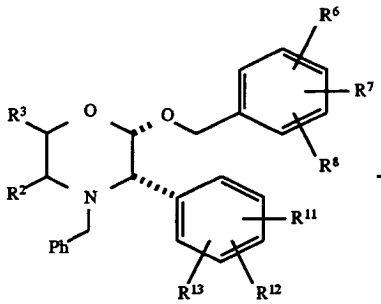
1) $(CF_3SO_2)_2O$, CCl_4
2) filter under N_2
3) concentrate, dissolve in toluene



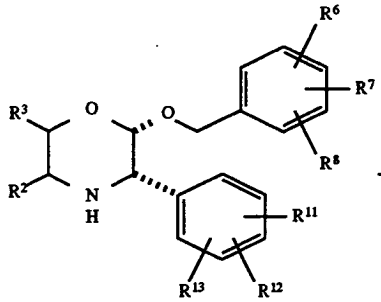
A



1) L-Selectride, −78° C.
2) A, −75° to −40° C., 5 hr

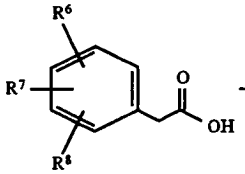


H_2, 10% Pd/C
EtOH, H_2O
or ACE-Cl
$ClCH_2CH_2Cl$
Δ

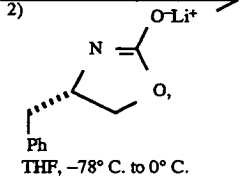


LG B DIEA
DMF or CH_3CN
Δ
or
B-CHO, $NaBH_3CN$
THF, MeOH

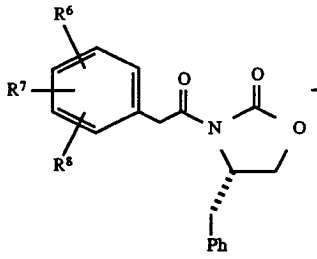
SCHEME 6



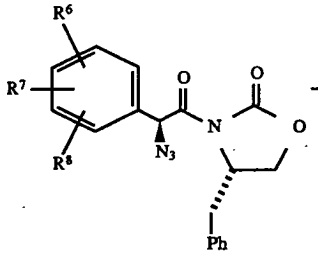
1) pivaloyl chloride, R_3N, ether, 0° C.
2)



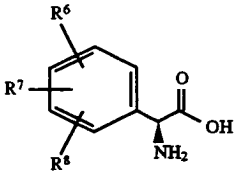
THF, −78° C. to 0° C.

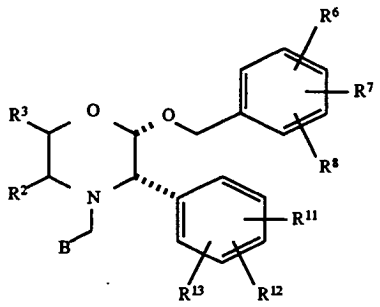


1) KHMDS, THF, −78° C.
2) $Ar'SO_2N_3$, THF, −78° C.
3) HOAc

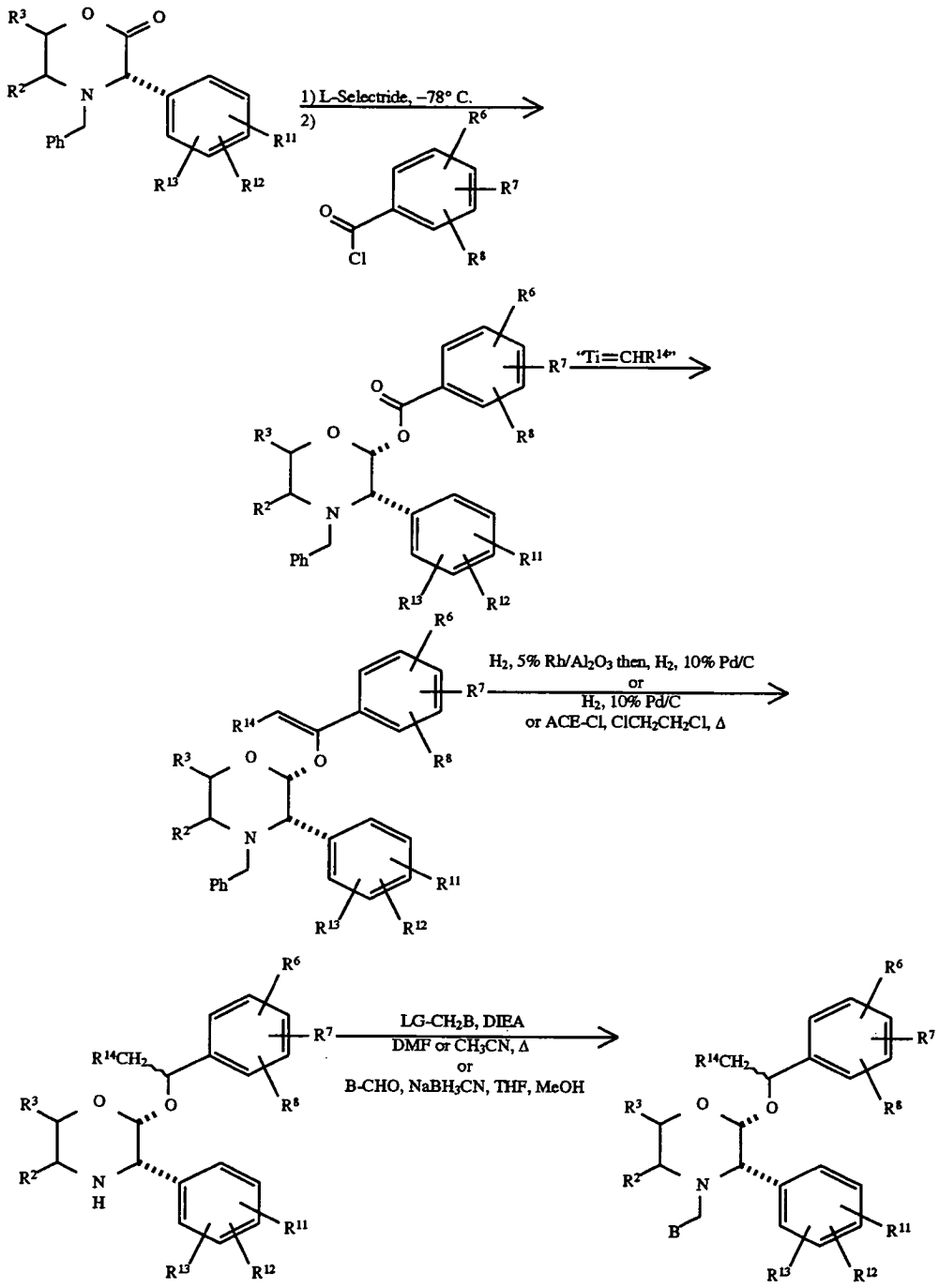


1) LiOH, THF/water
2) H_2, Pd/C, HOAc/water

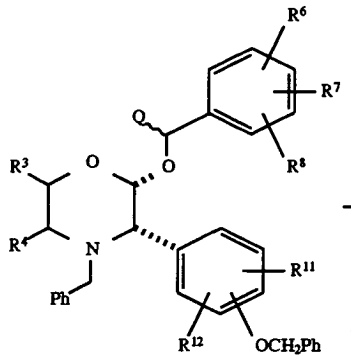




SCHEME 7

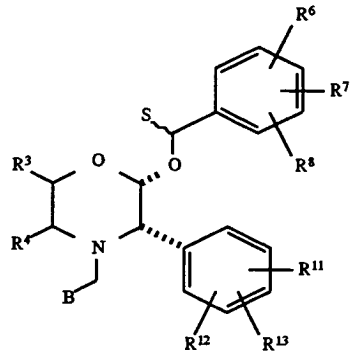

1) L-Selectride, −78° C.
2)
"Ti=CHR14"
H2, 5% Rh/Al2O3 then, H2, 10% Pd/C
or
H2, 10% Pd/C
or ACE-Cl, ClCH2CH2Cl, Δ
LG-CH2B, DIEA
DMF or CH3CN, Δ
or
B-CHO, NaBH3CN, THF, MeOH

SCHEME 8



Q = H_2 or R^{14}–CH =

Selective H_2
or
1) H_2, 10% Pd/C, iPrOH
2) TBS-Cl, DIEA, cat. DMAP, CH_2Cl_2
3) $PhCH_2Br$, DIEA, CH_3CN
4) TBAF, THF, 0° C.



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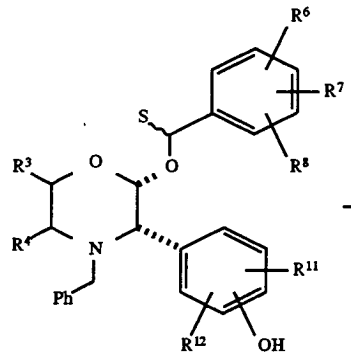
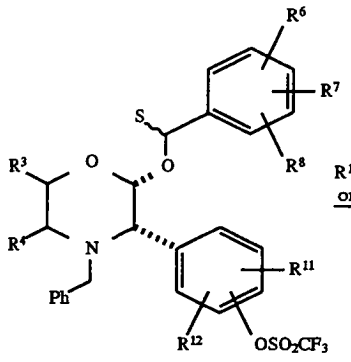
SCHEME 8



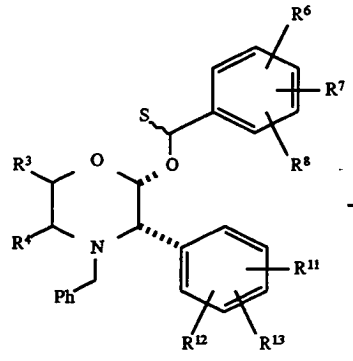
S = H_2 or R^{14}—CH_2—

Tf_2O
4-Me-2,6-di-tBu-pyridine
CH_2Cl_2, –78° C. to rt



S = H_2 or R^{14}—CH_2—

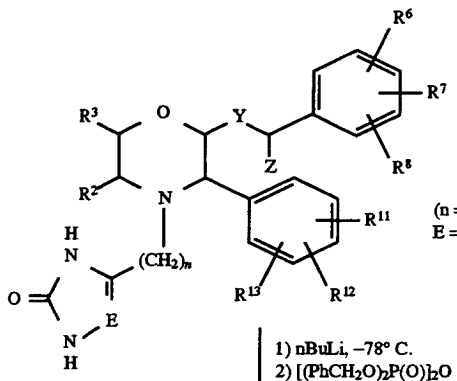
$R^{13}SnR_3$, or $R^{13}B(OH)_2$
or $R^{13}ZnX$ or CO, ROH
Pd-cat. or Ni-cat.



S = H_2 or R^{14}—CH_2—

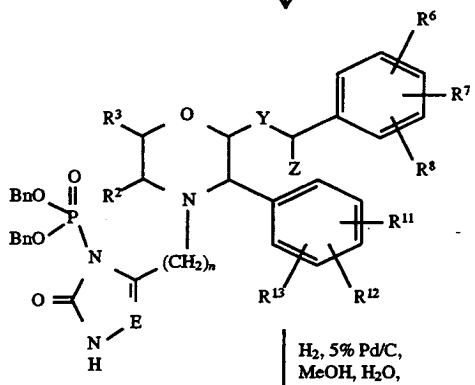
See Scheme 4 or 5

SCHEME 9

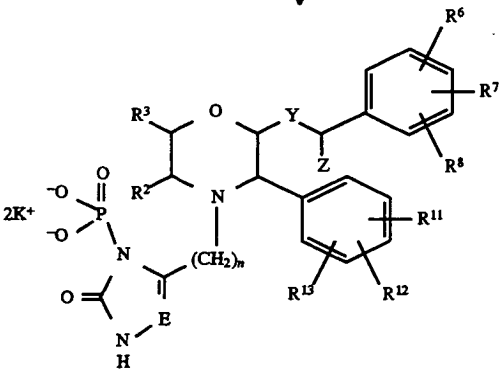


(n = 1–6
E = CH, N)

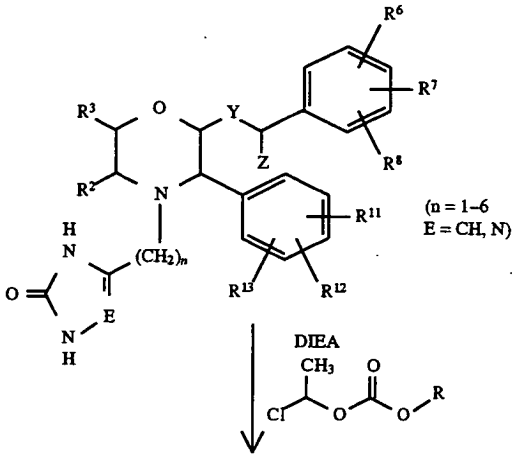
1) nBuLi, –78° C.
2) $[(PhCH_2O)_2P(O)]_2O$



H_2, 5% Pd/C,
MeOH, H_2O,
$KHCO_3$



SCHEME 10



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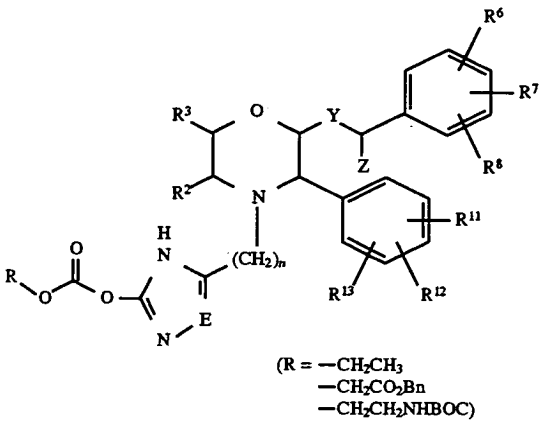
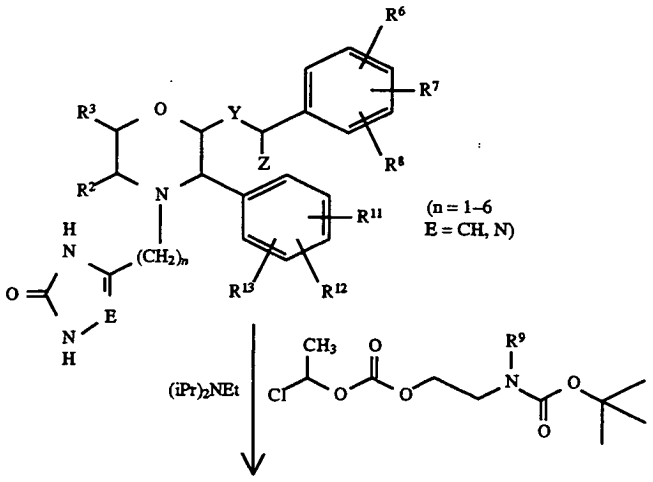
SCHEME 10



SCHEME 11



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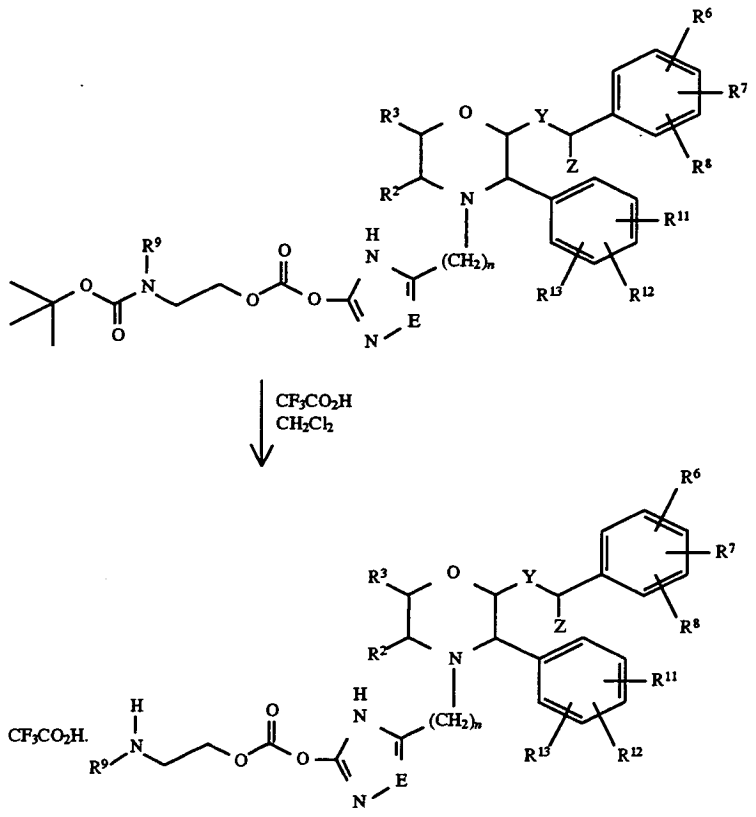
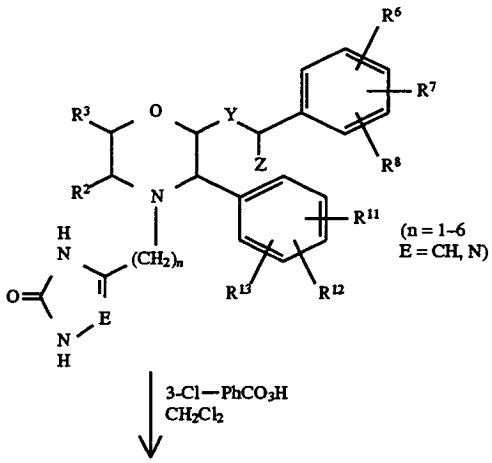
SCHEME 11



SCHEME 12



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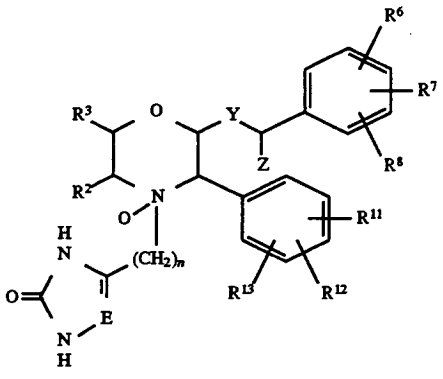
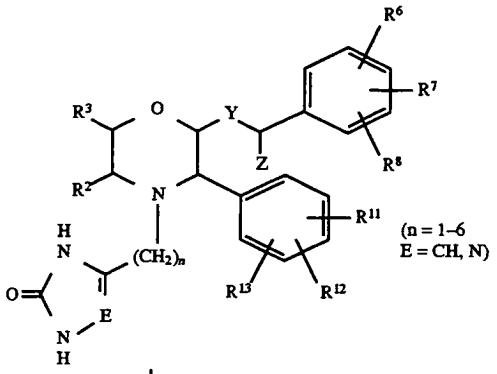
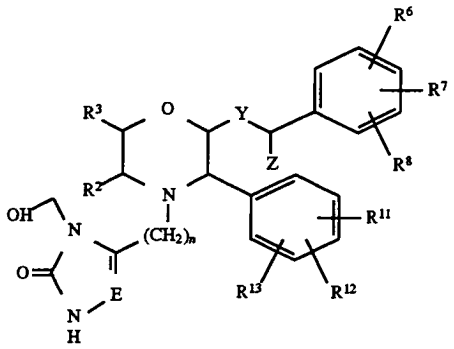
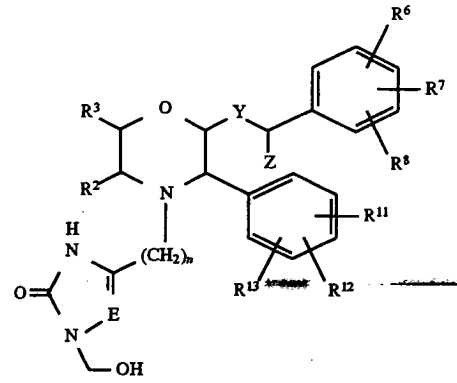
SCHEME 12



SCHEME 13







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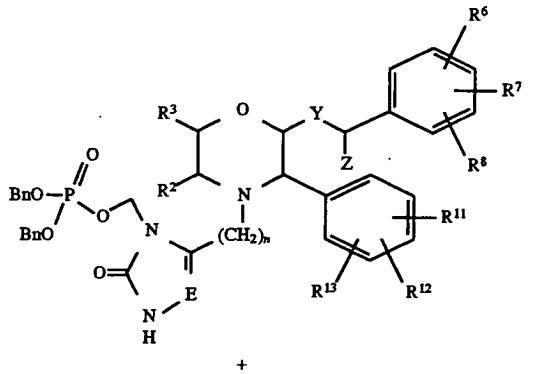

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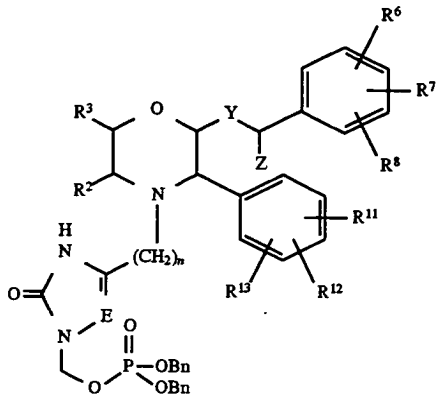
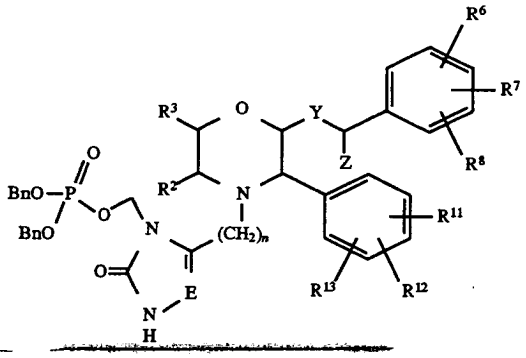
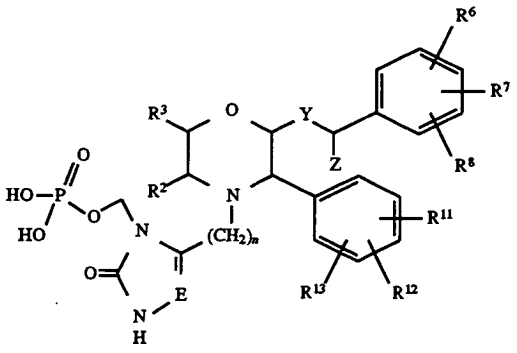
SCHEME 13

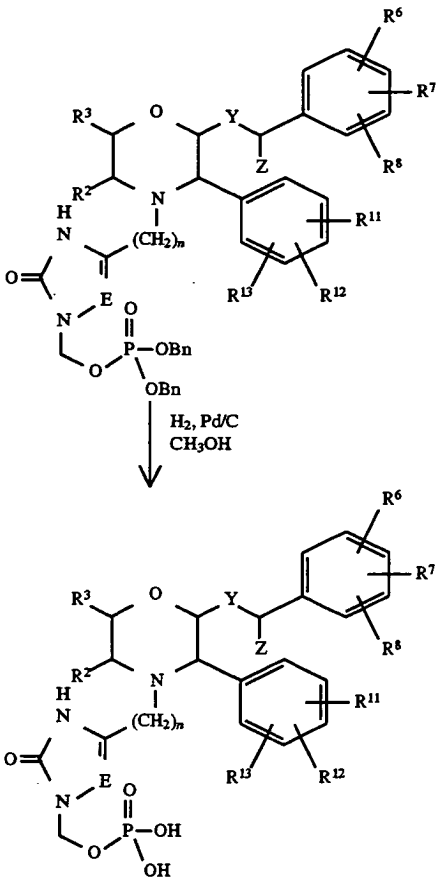


SCHEME 14





SCHEME 15



The compounds of the present invention in which Y=O may be prepared by the general route outlined in Scheme 1. Thus, the appropriately substituted α-bromophenylacetaldehyde, dimethyl acetal I (prepared using the method of Jacobs in *Journal of the American Chemical Society*, 1953, 75, 5500) may be convened to the dibenzyl acetal II by stirring I and a slight excess of a benzyl alcohol in the presence of an acid catalyst with concommitant removal of methanol. Alkylation of a substituted amino alcohol by benzyl bromide II may give N-alkyl amino alcohol III; use of a chiral amino alcohol would result in the formation of diastereomers and these may be separated at this (or at a later) stage using standard chromatographic methods. N-Alkylation or N-acylation of III may give the dialkyl- or acyl/alkyl-amino alcohol IV in which the group A—B may serve as a protecting group or be used as or elaborated into a substituent in the final target compound. Cyclization to give substituted morpholine V may be realized by warming a solution of IV and an acid catalyst. Diastereomers of V that may be formed may be separated using standard chromatographic methods. If A—B is a protecting group, it may be removed using known procedures (Greene, T. W., Wuts, P. G. M. Protective Groups in Organic Synthesis, 2nd ed., John Wiley & Sons, Inc., New York, 1991). If the preparation of I–V results in the formation of enantiomers, these may be resolved by alkylating or acylating V (A—B=H) with a chiral auxiliary, separating the diastereomers thus formed using known chromatographic methods, and removing the chiral auxiliary to give the enantiomers of V. Alternatively, the diastereomers of V may be separated via fractional crystallization from a suitable solvent of the diastereomeric salts formed by V and a chiral organic acid.

The compounds of the present invention in which $Y=CH_2$ may be prepared by the general route outlined in Scheme 2. Thus, the N-methoxy-N-methyl amide of a protected phenyl glycine VI (prepared from the carboxylic acid via the mixed anhydride according to the procedure of Rapoport in *Journal of Organic Chemistry*, 1985, 50, 3972) may be used to acylate the lithium enolate of methyl diethylphosphonate to give the ketophosphonate VII. The sodium salt of VII may be condensed with an appropriately substituted benzaldehyde to give the α,β-unsaturated ketone VIII. Reduction of the ketone and removal of the t-butylcarbamate protecting group may give amino alcohol IX; diastereomers that may form may be separated at this (or at a later) stage using standard chromatographic techniques. Williamson etherification of IX using a substituted chloroacetate, followed by warming, may result in the formation of morpholinone X. Reduction of the double bond and amide carbonyl may be accomplished in a straightforward manner to give the substituted morpholine XI. If the preparation of VI–XI results in the formation of enantiomers, these may be resolved by alkylating or acylating XI (A—B=H) with a chiral auxiliary, separating the diastereomers thus formed using known chromatographic methods, and removing the chiral auxiliary to give the enantiomers of XI. Alternatively, the diastereomers of XI may be separated via fractional crystallization from a suitable solvent of the diastereomeric salts formed by XI and a chiral organic acid. If it is desired that A—B is other than H, the morpholine nitrogen of XI may be further functionalized using standard methods for the alkylation or acylation of secondary amines. If it is desired that R^2 is other than H, morpholinone X may be elaborated into the carbinolcarbamate (A—B=RO_2C, R^2=OH), an intermediate that could be alkylated and would allow for variation in R^2.

The compounds of the present invention in which Y=O may also be prepared by the general route outlined in Scheme 3. Thus, the appropriately substituted a-bromoacetaldehyde, dimethyl acetal (prepared using the method of Jacobs in *Journal of the American Chemical Society*, 1953, 75, 5500) may be converted to the acetal by stirring and a slight excess of the appropriate alcohol in the presence of an acid catalyst with concommitant removal of methanol. Alkylation of a substituted amino alcohol by a bromide may give the N-alkyl amino alcohol; use of a chiral amino alcohol would result in the formation of diastereomers and these may be separated at this (or at a later) stage using standard chromatographic methods. N-Alkylation or N-acylation may give the dialkyl- or acyl/alkyl-amino alcohol in which the group A—B may serve as a protecting group or be used as or elaborated into a substituent in the final target compound. Cyclization to give substituted morpholine may be realized by warming a solution with an acid catalyst. Diastereomers that may be formed may be separated using standard chromatographic methods. If A—B is a protecting group, it may be removed using known procedures (Greene, T. W., Wuts, P. G. M. Protective Groups in Organic Synthesis, 2nd ed., John Wiley & Sons, Inc., New York, 1991). If the preparation of such compounds results in the formation of enantiomers, these may be resolved by alkylating or acylating the final product (A—B=H) with a chiral auxiliary, separating the diastereomers thus formed using known chromatographic methods, and removing the chiral auxiliary to give the desired enantiomers. Alternatively, the diastereomers may be separated via fractional crystallization from a suitable solvent of the diastereomeric salts formed by the compound of a chiral organic acid.

One method of synthesizing enantiomerically pure substituted morpholines is illustrated in Scheme 4. Protection of enantiomerically pure phenylglycine as the N-benzyl deriva-

tive followed by double alkylation with a 1,2-dibromoethane derivative leads to the morpholinone. Reduction with an active hydride reagent such as diisobutyl aluminum hydride, lithium aluminum hydride, lithium tri(sec-butyl)-borohydride (L-Selectride®) or other reducing agents leads predominantly to the 2,3-trans morpholine derivatives. Alkylation of the alcohol, removal of the protecting group on nitrogen (for example, with a palladium hydrogenation catalyst or with 1-chloroethyl chloroformate (Olofson in *J. Org. Chem.*, 1984, 2081 and 2795), and alkylation of the nitrogen (wherein in A—B—CH_2— or A—B—CHO= appropriate definitions of A—B are present) produces the 2,3-trans compounds.

One method of producing enantiomerically pure 2,3-cis morpholines is illustrated in Scheme 5. In the first step, formation of the trifluoromethane-sulfonate ester of the appropiate benzyl alcohol (especially benzyl alcohols which are substituted with electron-withdrawing groups such as —NO_2, —F, —Cl, —Br, —COR, —CF_3, etc) is carried out in the presence of an unreactive base, in an inert solvent. Other leaving groups such as iodide, mesylate, tosylate, p-nitrophenylsulfonate and the like may also be employed. Appropriate bases include 2,6-di-t-butylpyridine, 2,6-di-t-butyl-4-methyl-pyridine, diisopropylethylamine, potassium carbonate, sodium carbonate, and the like. Suitable solvents include toluene, hexanes, benzene, carbon tetrachloride, dichloromethane, chloroform, dichloroethane, and the like and mixtures thereof. The filtered solution of the triflate is then added to a solution of the intermediate formed when the morpholinone is contacted with an active hydride reagent such as diisobutyl aluminum hydride, lithium aluminum hydride, or lithium tri(sec-butyl)-borohydride (L-Selectride®) at low temperature, preferably from −78° C. to −20° C. After several hours at low temperature, workup and purification provides predominantly 2,3-cis substituted products, which may be carried on to final compounds as shown in Scheme 5.

Enantiomerically pure phenylglycines substituted on the phenyl ring may be prepared by the procedure shown in Scheme 6 (D. A. Evans, et al. *J. Am. Chem. Soc.*, 1990, 112, 4011).

Methods for preparing the nitrogen alkylating agents A—B—CH_2-LG (wherein "LG" indicates an appropriately suitable leaving group) used in Scheme 4 and Scheme 5 are based on known literature methods (for A—B=3-(1,2,4-triazolyl) or 5-(1,2,4-triazol-3-one)-yl and LG=Cl, see Yanagisawa, I.; Hirata, Y.; Ishii, Y. *Journal of Medicinal Chemistry*, 27, 849 (1984); for A—B=4-((2H)-imidazol-2-one)-yl or 5-(4-ethoxycarbonyl-(2H)-imidazol-2-one)-yl and X=Br, see Ducschinsky, R., Dolan, L. A. *Journal of the American Chemical Society*, 70, 657 (1948)).

One method of producing enantiomerically pure 2,3-cis morpholines that are substituted at the α-position of the C2 benzyl ether is shown in Scheme 7. Thus, a substituted 2-morpholinone (prepared as described in Scheme 4) is reacted with an active hydride reagent, such as diisobutylaluminum hydride, lithium aluminum hydride, or lithium tri(sec-butyl)borohydrdide and the resulting reaction intermediate is quenched with a substituted benzoyl halide, anhydride, or other activated acyl transfer reagent. Aqueous work-up affords the 2-benzoyloxy compound shown in Scheme 7. This compound is converted to the corresponding enol ether using a "titanium ylide" generated from reagents such as μ-chloro-μ-methylene-[bis(cyclopentadienyl) titanium]dimethylamluminum ("Tebbe Reagent", Tebbe, F. N., Parshall, G. W., Reddy, G. S., *Journal of the American Society*, 100, 3611 (1978)), dimethyl titanocene (Petasis, N. A., Bzowej, E. L. *Journal of the American Chemical Society*, 112, 6392 (1990)) or the reagent prepared by the reduction of 1,1-dibromoalkanes with zinc and titanium tetrachloride in the presence of N,N,N',N'-tetramethylethylenediamine (Takai, K. et. al., *Journal of Organic Chemistry*, 52, 4412 (1987)). The resulting enol ether is reduced to its saturated analog by hydrogenation in the presence of a rhodium based catalyst, such as rhodium on alumina or on carbon; if concomitant removal of the N-benzyl group on the morpholine nitrogen is desired, the hydrogenation may be carried out in the presence of palladium on carbon catalyst. If diastereomers are obtained at this juncture, they may be separated using chromatographic methods or by recrystallization of the mixture of diastereomers. Elaboration of the morpholines so obtained to the final product is carried out in manners analogous to those described in Schemes 4 and 5.

Methods by which the substitution on the C-3 phenyl ring of the morpholines of the present invention may be introduced or altered is shown in Scheme 8. Thus, a substituted morpholine may be prepared as described in Scheme 4, 5, or 7 from an enantiomerically pure benzyloxy-substituted aryl glycine (prepared as described in the literature (e.g. L-p-benzyloxyphenylglycine may be prepared according to the procedure of Kamiya, et al. *Tetrahedron*, 35, 323 (1979)) or using the methods described in Scheme 6). Selective cleavage of the benzyl ether via hydrogenolysis or nonselective hydrogenolysis followed by the synthetic sequence shown in Scheme 8 may afford a suitably protected phenolic intermediate. The phenol may be converted to the corresponding aryl triflate (as shown, or using N-phenyltrifluoromethanesulfonimide in the presence of a tertiary amine base in methylene chloride) and the triflate converted to the desired functional group using the palladium- or nickel-catalyzed methods described in Ritter, *Synthesis*, 735 (1993) (and refs. therein). Elaboration to the desired final product may be carried out as described in Scheme 4 or 5.

The parent compounds prepared above are converted to their prodrug counterparts by alkylation, acylation, phosphorylation or suffonylation to give ether, ester, phosphate or suffonate derivatives (wherein the parent compounds bear an —X substitutent as defined above) by the general procedures referenced herein, or reasonable modifications thereof.

In particular, as depicted in Scheme 9, treatment of, for example, a triazolone or imidazolone-containing tachykinin antagonist with a suitable base, such as n-butyllithium, sodium hydride, potassium hydride, lithium hexamethyldisilazide, sodium hexamethyldisilazide, potassium hexamethyldisilazide or lithium diisopropylamide in THF at low temperature followed by addition of an appropiate phosphoryl transfer reagent, for example tetrabenzyl pyrophosphate, dibenzyl phosphochloridate or dibenzyl phosphofluoridate provides an intermediate with a protected phosphoryl group. Following purification, for example by gravity silica gel chromatography or by reverse phase high pressure liquid chromatography, the dibenzyl ester may be converted into the desired product by hydrogenolysis, for example with hydrogen gas in the presence of palladium on carbon in the presence of two equivalents of a suitable salt forming agent, such as sodium bicarbonate (to prepare the disodium salt of the phosphoramidate product) or potassium bicarbonate (to prepare the dipotassium salt of the product). The product may be purified by crystallization or by normal or reverse phase chromatography.

As depicted in Scheme 10, treatment of, for example, a triazolone or imidazolone-containing tachykinin antagonist with a suitable base, such as diisopropylethylamine, 2,6-dimethylpyridine or triethylamine and 1-chloroethyl ethyl

carbonate (wherein R may be ethyl, —$CH_2CO_2CH_2$phenyl, or —CH_2CH_2NH-BOC) in a compatible solvent such as toluene or dichloroethane, followed by heating the mixture at reflux for 12–24 hr, provides the corresponding O-alkylcarbonate product (insted of the expected N-alkoxycarbonylalkyl compound), which may be purified by flash chromatography.

Similarly, the same substrate may be treated with the functionalized carbonate given in Scheme 11 under similar conditions, such as refluxing in toluene in the presence of diisopropylethylamine, 2,6-dimethylpyridine or triethylamine to provide the N-Boc protected intermediate. Cleavage of the Boc group, for example with trifluoroacetic acid in methylene chloride or with hydrogen chloride in ethyl acetate provides the corresponding salt of the prodrug product.

Generation of the N-oxide prodrug of the aforementioned morpholine tachykinin antagonists may be achieved as shown in Scheme 12 simply by treatment with an oxygen-transfer agent, such as a peracid, such as 3-chloroperoxybenzoic acid or trifluoromethylperacetic acid, or with hydrogen peroxide or alkyl hydroperoxides such as t-butyl hydroperoxide in the presence of a transition metal catalyst, or with Caro's acid (H_2SO_5).

Compounds containing linking groups between the heterocycle and the phosphoryl group may also be prepared, for example as illustrated in Scheme 13 (see S. A. Varia, S. Schuller, K. B. Sloan, and V. J. Stella, *J. Pharm. Sci.*, 73, 1068–1073 (1984)). Treatment of the parent compound with an aliphatic aldehyde, for example aqueous formaldehyde, provides the corresponding hydroxymethyl derivatives, which after conversion to the chloride with phosphorus trichloride, may be treated with silver dibenzyl phosphate. The resulting protected phosphates may be separated by conventional means, for example silica gel chromatography. The purified products may then be converted to the free phosphoric acids as depicted in Schemes 14 and 15, by treatment with a reducing agent such as hydrogen gas in the presence of pallidium on carbon.

The object compounds of Formula I obtained according to the reactions as explained above may be isolated and purified in a conventional manner, for example, extraction, precipitation, fractional crystallization, recrystallization, chromatography, and the like.

The compounds of the present invention are capable of forming salts with various inorganic and organic acids and bases and such salts are also within the scope of this invention. Examples of such acid addition salts include acetate, adipate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, ethanesulfonate, fumarate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, methanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, oxalate, pamoate, persulfate, picrate, pivalate, propionate, succinate, tartrate, tosylate, and undecanoate. Base salts include ammonium salts, alkali metal salts such as sodium, lithium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, ornithine and so forth. Also, the basic nitrogen-containing groups may be quaternized with such agents as: lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl; diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; aralkyl halides like benzyl bromide and others. The non-toxic physiologically acceptable salts are preferred, although other salts are also useful, such as in isolating or purifying the product.

The salts may be formed by conventional means, such as by reacting the free base form of the product with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is removed in vacuo or by freeze drying or by exchanging the anions of an existing salt for another anion on a suitable ion exchange resin.

Although the reaction schemes described herein are reasonably general, it will be understood by those skilled in the art of organic synthesis that one or more functional groups present in a given compound of formula I may render the molecule incompatible with a particular synthetic sequence. In such a case an alterative route, an altered order of steps, or a strategy of protection and deprotection may be employed. In all cases the particular reaction conditions, including reagents, solvent, temperature, and time, should be chosen so that they are consistent with the nature of the functionality present in the molecule.

As one skilled in the art will recognize, Examples 1–93 describe the prepartion of various parent compounds, whereas Examples 94–96 detail the prepartion of specific prodrugs of some of the parent compounds. Accordingly, the methodology presented in Examples 94–96 is readily adapted without undue experimentation to the preparation of the compounds of the present invention, including prodrugs of the parent compounds of Examples 1–93.

The following examples are given for the purpose of illustrating the present invention and shall not be construed as being limitations on the scope or spirit of the instant invention.

EXAMPLE 1

(±)-α-Bromo-phenylacetaldehyde, 3,5-bis(trifluoromethyl)benzyl acetal

A solution of 2.50 g (10.2 mmol) of α-bromophenylacetaldehyde, dimethyl acetal, 8.00 g (32.8 mmol) of 3,5-bis(trifluoromethyl)benzyl alcohol and 0.50 g (2.6 mmol) of p-toluenesulfonic acid monohydrate in 10 mL of toluene was stirred under vacuum (35 mmHg) at rt for 3 days. The reaction mixture was partitioned between 100 mL of ether and 50 mL of saturated aqueous sodium bicarbonate solution and the layers were separated. The organic layer was washed with 25 mL of saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. Flash chromatography on 200 g of silica gel using 9:1 v/v hexane/methylene chloride as the eluant afforded 5.41 g (81%) of the title compound as a solid, mp 79°–82° C.: ^{1}H NMR 4.47 and 4.62 (AB q, 2H, J=12.5), 4.78–4.93 (2H), 5.09 and 5.21 (AB q, 2H, J=7.7), 7.31–7.44 (m, 7H), 7.70 (app s, 1H), 7.82 (app s, 1H), 7.84 (app s 2H); IR (thin film) 1363, 1278, 1174, 1130, 704, 682.

Analysis Calcd for $C_{26}H_{17}BrF_{12}O_2$: C, 46.76; H, 2.23; Br, 11.64; F, 33.70. Found: C, 46.65; H, 2.56; Br, 11.94; F, 34.06.

EXAMPLE 2

(±)-N-(2-Hydroxyethyl)-phenylglycinal, 3,5-bis-(trifluoromethyl)benzyl acetal

A solution of 1.50 g (2.2 mmol) of (±)-α-bromophenylacetaldehyde, 3,5-bis(trifluoromethyl)-benzyl acetal (Example 1), 100 mg (0.67 mmol) of sodium iodide

and 3 mL of ethanolamine in 6 mL of isopropanol was heated at reflux for 20 h. The solution was cooled and concentrated to ~25% the original volume in vacuo. The concentrated solution was partitioned between 50 mL of ether and 20 mL of 2N aqueous sodium hydroxide solution and the layers were separated. The organic layer was washed with 20 mL of saturated aqueous sodium chloride solution, dried over magnesium sulfate and concentrated in vacuo. Flash chromatography on 50 g of silica gel using 65:35 v/v ether/hexane as the eluant afforded 1.18 g (83%) of the title compound as an oil: ^{1}H NMR 2.66 (br s, 2H), 2.61 and 2.68 (ddAB q, 2H, J_{AB}=12.4, $J_{2,61}$=6.8, 6.2, $J_{2,68}$ =6.2, 6.2), 3.57 and 3.66 (ddAB q, 2H, J_{AB}=10.8, $J_{3,57}$=6.2, 6.2), $J_{3,66}$=6.8, 6.2), 4.02 (d, 1H, J=7.0), 4.37 and 4.64 (AB q, 2H, J=12.5), 4.80 and 4.87 (AB q, 2H, J=12.8), 4.87 (d, 1H, J=7.0), 7.31–7.40 (7H), 7.73 (app s, 1H), 7.81 (app s, 3H);

IR (neat)3342, 1456, 1373, 1278, 1173, 1128, 704, 682;

FAB-MS 650(M+1)$^+$.

Analysis Calcd for $C_{28}H_{23}F_{12}NO_3$: C, 51.78; H, 3.57; N, 2.16; F, 35.11. Found: C, 51.80; H, 3.67; N, 2.10; F, 35.41.

EXAMPLE 3

(±)-N-(2-Hydroxyethyl)-N-(prop-2-enyl)-phenylglycinal, 3,5-bis(trifluoromethyl)benzyl acetal

A mixture of 1.45 g (2.2 mmol) of (±)-N-(2-hydroxyethyl) -phenylglycinal, 3,5-bis-(trifluoromethyl)benzyl acetal (Example 2), 1.0 g (7.2 mmol) of potassium carbonate, 3.0 mL (35.0 mmol) of allyl bromide and 15 mL of ethanol was stirred at 60° C. for 20 h. The mixture was cooled, partitioned between 100 mL of ether and 25 mL of water and the layers were separated. The organic layer was dried over magnesium sulfate. The aqueous layer was extracted with 100 mL of ether; the ether extract was dried and combined with the original organic layer. The combined organic layers were concentrated in vacuo. Flash chromatography on 50 g of silica gel using 4:1 v/v hexane/ether as the eluant afforded 1.36 g (88%) of the title compound as an oil: ^{1}H NMR 2.40 (dt, 1H, J=13.2, 2.8), 2.93–3.08 (3H), 3.30 (ddt, 1H, J=12.0, 2.8, 1.6), 3.54 (br m, 2H), 3.65 (dt, 1H, J=10.0, 2.8), 4.23 (d, 1H, J=8.4), 4.52 and 4.58 (AB q, 2H, J=12.4), 4.85 and 4.95 (AB q, 2H, J=12.4), 5.25 (d, 1H, J=9.6), 5.28 (d, 1H, J=16.4), 5.39 (d, 1H, J=8.4), 5.81 (m, 1H), 7.24–7.40 (7H), 7.68 (s 1H), 7.83 (s, 1H), 7.86 (s, 2H);

IR (neat) 3457, 1362, 1278, 1174, 1132, 1056, 759, 705, 682; FAB-MS 690(M+1)$^+$.

Analysis Calcd for $C_{31}H_{27}F_{12}NO_3$: C, 53.99; H, 3.95; N, 2.03; F, 33.07. Found: C, 54.11; H, 4.08; N, 1.78; F, 32.75.

EXAMPLE 4

(±)-2-(3,5-Bis(trifluoromethyl)benzyloxy)-3-phenylmorpholine

Step A: A solution of 850 mg (1.2 mmol) of (±)-N-(2-hydroxyethyl)-N-(prop-2-enyl)-phenyl-glycinal, 3,5-bis (trifluoromethyl)benzyl acetal (Example 3) and 700 mg (3.7 mmol) of p-toluenesulfonic acid monohydrate in 15 mL of toluene was heated at reflux for 1.5 h. The reaction mixture was cooled and partitioned between 100 mL of ether and 25 mL of saturated aqueous sodium bicarbonate solution. The layers were separated; the organic layer was washed with 25 mL of saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. Flash chromatography on 30 g of silica gel using 50:1 v/v hexane/ether as the eluant afforded 426 mg (78%) of the N-allyl morpholines which were used in the next step without further purification.

Step B: A 50 mL 2-necked flask, equipped with a stopper and a short path distillation apparatus, was charged with a solution of the N-allyl morpholines (Example 4, Step A) (540 mg, 1.2 mmol)) and 80 mg (0.09 mmol) tris (triphenylphosphine)rhodium chloride (Wilkinson's catalyst) in 25 mL of 4:1 v/v acetonitrile/water. The reaction mixture was heated to boiling and solvent was allowed to distill from the reaction mixture. The volume of the reaction mixture was maintained between 10 and 20 mL by adding solvent through the stoppered inlet. After 1 h and 4 h, the reaction was treated with additional 80 mg portions of the Wilkinson's catalyst. After 6 h, the reaction mixture cooled and partitioned between 75 mL of ether and 50 mL of water. The layers were separated and the organic layer was dried over magnesium sulfate. The aqueous layer was extracted with 75 mL of ether; the extract was dried and combined with the original organic layer. The combined organic layers were concentrated in vacuo. Flash chromatography on 35 g of silica gel using 1:1 v/v ether/hexane as the eluant afforded 200 mg of trans-isomer and 130 mg of a mixture of cis- and trans-isomers (68% total). Chromatography of the mixture on 8 g of silica gel using 4:1 v/v hexane/ether as the eluant afforded 64 mg of cis and 57 mg of a mixture of the cis- and trans-isomers of the title compound.

For trans: ^{1}H NMR 2.03 (br s, 1H), 2.94 (ddd, 1H, J=11.0, 2.5, 2.5), 3.08 (dt, 1H, J=11.0, 3.2), 3.71 (d, 1H, J=7.0), 3.83 (dt, 1H, J=11.2, 2.8), 4.05 (ddd, 1H, J=11.2, 3.2, 3.2), 4.43 (d, 1H, J=7.0), 4.53 and 4.88 (AB q, 2H, J=13.3), 7.26–7.45 (7H), 7.70 (s, 1H);

IR (neat) 3333, 2859, 1456, 1374; 1278, 1173, 1131, 1082, 757, 702, 682; FAB-MS 406(M+1)$^+$.

Analysis Calcd for $C_{19}H_{17}F_6NO_2$: C, 56.30; H, 4.23; N, 3.46; F, 28.12. Found: C, 56.39; H, 4.28; N, 3.36; F, 28.32.

For cis: ^{1}H NMR 2.10 (br s, 1H), 3.13 (dd, 1H, J=12.4, 3.0), 3.26 (dt, 1H, J=12.4, 3.6), 3.65 (dd, 1H, J=11.6, 3.6), 4.07 (dt, 1H, J=11.6, 3.0), 4.14 (d, 1H, J=2.4), 4.52 and 4.82 (AB q, 2H, J=13.6), 4.76 (d, 1H, J=2.4), 7.30–7.42 (6H), 7.70 (s, 1H), FAB-MS 406(M+1)$^+$.

EXAMPLE 5

(±)-2-(3,5-Bis(trifluoromethyl)benzyloxy)-3-phenyl-4-methylcarboxamido morpholine

A solution of 105 mg (0.26 mmol) of the trans-isomer of (±)-2-(3,5-bis(trifluoromethyl)benzyloxy)-3-phenyl-morpholine (Example 4) and 0.09 mL (0.50 mmol) of N,N-diisopropylethylamine in 3 mL of acetonitrile was treated with 90 mg (0.50 mmol) of iodoacetamide and the resulting solution was stirred at rt for 16 h. The solution was concentrated in vacuo and the residue was partitioned between 20 mL of ethyl acetate and 10 mL of 0.5N aqueous potassium hydrogen sulfate solution. The layers were separated; the organic layer was washed with 10 mL of 5% aqueous sodium thiosulfate solution, 10 mL of saturated aqueous sodium bicarbonate solution, 10 mL of saturated aqueous sodium chloride solution, dried over magnesium sulfate and concentrated in vacuo. Flash chromatography on 5 g of silica gel using 2:1 v/v ethyl acetate/hexane as the eluant afforded 99 mg (82%) of the trans-isomer of the title compound as an oil: ^{1}H NMR 2.56 (dt, 1H, J=3.2, 11.6), 2.67 and 3.16 (AB q, 2H, J=16.4), 2.96 (dt, 1H, J=12.0, 1.6), 3.30 (d, 1H, J=7.0), 3.86 (dt, 1H, J=3.2, 12.0), 4.08 (ddt, 1H, J=11.6, 3.2, 1.6), 4.48 and 4.84 (AB q, 2H, J= 13.2), 4.49 (d, 1H, J=7.0), 5.98 (br s, 1H), 6.83 (br s, 1H), 7.33 (app s, 7H), 7.70 (s, 1H);

IR (neat) 3445, 2838, 1682, 1278, 1173, 1132, 760, 704, 682; FAB-MS 463 (M+1)$^+$.

Analysis Calcd for $C_{21}H_{20}F_6NO_3$: C, 54.54; H, 4.36; N, 6.06; F, 24.65. Found: C, 54.54; H, 4.52; N, 5.61; F, 24.45.

A similar experiment was carried out on 40 mg (0.99 mmol) of the cis-isomer of (±)-2-(3,5-bis-(trifluoromethyl) benzyloxy)-3-phenyl-morpholine (Example 4) using 0.035 mL (0.2 mmol) of N,N-diisopropylethylamine and 37 mg (0.2 mmol) of iodoacetamide in the reaction. Work-up and flash chromatography afforded 30 mg (65%) of the cis-isomer of the title compound as an oil:

^{1}H NMR 2.54 and 3.04 (AB q, 2H, J=16.8), 2.63 (dt, 1H, J=3.6, 12.0), 3.04 (d, 1H, J=11.6), 3.65 (d, 1H, J=2.8), 3.71 (ddt, 1H, J=11.6, 3.2, 1.2), 4.21 (dt, 1H, J=11.6, 2.4), 4.44 and 4.89 (AB q, 2H, J=13.6), 4.71 (d, 1H, J=2.8), 5.86 (br s, 1H), 7.15 (br s, 1H), 7.27–7.45 (7H), 7.73 (s, 1H); FAB-MS 463(M+1)$^+$.

EXAMPLE 6

(±)-2-(3,5-Bis(trifluoromethyl)benzyloxy)-3-phenyl-4-(methoxycarbonylmethyl)morpholine

A solution of 150 mg (0.37 mmol) of the trans-isomer of (±)-2-(3,5-bis(trifluoromethyl)benzyloxy)-3-phenyl morpholine (Example 4) and 0.18 mL (1.00 mmol) of N,N-diisopropyl-ethyl-amine in 2 mL of acetonitrile was treated with 0.095 mL (1.00 mmol) of methyl bromoacetate and the resulting solution was stirred at rt for 20 h. The solution was concentrated in vacuo and the residue was partitioned between 20 mL of ethyl acetate and 5 mL of 0.5N aqueous potassium hydrogen sulfate solution. The layers were separated; the organic layer was washed with 10 mL of saturated aqueous sodium chloride solution, dried over magnesium sulfate and concentrated in vacuo. Flash chromatography on 10 g of silica gel using 4:1 v/v hexanes/ether as the eluant afforded 164 mg (93%) of the trans-isomer of the title compound as an oil: ^{1}H NMR 2.79 (dt, 1H, J=3.2, 11.2), 2.93 (dt, 1H, J=11.2, 1.6), 3.52 (d, 1H, J=7.2), 3.63 (s, 3H), 3.92 (dt, 1H, J=2.8, 11.6), 4.04 (ddd, 1H, J=11.6, 3.2, 1.6), 4.45 and 4.84 (AB q, 2H, J=13.2), 4.46 (d, 1H, J=7.2), 7.31–7.38 (m, 6H), 7.68 (s, 1H); IR (neat) 2861, 1744, 1455, 1375, 1346, 1278, 1170, 887, 759, 704, 682; FAB-MS 478(M+1)$^+$.

Analysis Calcd for $C_{22}H_{21}F_6NO_4$: C, 55.35; H, 4.43; N, 2.93; F, 23.88. Found: C, 55.74; H, 4.50; N, 2.79; F, 24.01.

EXAMPLE 7

N-Methoxy-N-methyl-(N-t-butoxycarbonyl)-phenylglycinamide

A solution of 20.0 g (79.7 mmol) of (N-t-butoxycarbonyl) phenylglycine in 150 mL of ethyl acetate at −10° C. was treated with 8.8 mL (79.7 mmol) of 4-methylmorpholine. Isobutylchloroformate (10.3 mL, 79.7 mmol) was added dropwise over 10 minutes maintaining the temperature at −10° C.; the resulting suspension was stirred cold for 15 min. The mixture was treated with 11.6 g (119.0 mmol) of N,O-Dimethyl-hydroxylamine•HCl. A second portion of 4-methylmorpholine (13.0 mL, 119.0 mmol) was added and the reaction was stirred at −10° C. for 15 min and at 25° C. for 2 h. The reaction mixture was partitioned between 100 mL of ethyl acetate and 100 mL of 10% aqueous citric acid solution and the layers were separated. The organic layer was washed with 100 mL of saturated aqueous sodium bicarbonate solution, 100 mL of saturated aqueous ammonium chloride solution, dried over magnesium sulfate and concentrated in vacuo. Crystallization from hexanes at −20° C. for 72 h afforded 8.0 g (34%) of the title compound as a solid: ^{1}H NMR 1.40 (s, 9H), 3.20 (s, 3H), 3.40 (s, 3H), 5.80 (m, 2H), 7.40 (m, 5H).

EXAMPLE 8

Diethyl (2-oxo-3-t-butoxycarbamido-3-phenyl)-propylphosphonate

A solution of 7.45 mL (51.0 mmol) of diethyl methylphosphonate in tetrahydrofuran at −78° C. was treated with 31.8 mL (51.0 mmol) of 1.6M n-butyllithium in hexanes solution and the resulting mixture was stirred cold for 30 min. A solution of 4.0 g (14.0 mmol) of N-methoxy-N-methyl-(N-t-butoxycarbonyl)phenylglycinamide (Example 7) in 20 mL of tetrahydrofuran was added and the reaction was stirred at −78° C. for 15 min and at 25° C. for 15 min. The reaction was quenched with 150 mL of saturated aqueous ammonium chloride solution, diluted with 300 mL of ethyl acetate, and the layers were separated. The organic layer was dried over magnesium sulfate and concentrated in vacuo. Hash chromatography on silica gel using 7:3 v/v then 4:1 v/v ethyl acetate/hexanes as the eluant afforded 4.8 g (92%) of the title compound as an oil: ^{1}H NMR 1.20–1.42 (15H), 2.84 (dd, 1H), 3.20 (dd, 1H), 4.00–4.20 (m, 4H), 5.50 (d, 1H), 5.94 (br s, 1H), 7.32 (m, 5H).

EXAMPLE 9

N-t-Butoxycarbonyl-1-phenyl-2-oxo-4-(3,5-bis(trifluoromethyl)phenyl)-but-3-enamine

A solution of 4.80 g (12.5 mmol) of diethyl (2-oxo-3-t-butoxycarbamido-3-phenyl)propylphosphonate (Example 8) in 20 mL of THF was added dropwise to a suspension of 1.05 g (26.3 mmol, 60% dispersion in mineral oil) of sodium hydride in 30 mL of tetrahydrofuran at 0° C. After 15 min, 2.06 mL (12.5 mmol) of 3,5-bis(trifluoromethyl) benzaldehyde was slowly added and the resulting mixture was stirred cold for 15 min. The reaction was quenched with 50 mL of saturated aqueous ammonium chloride solution, diluted with 50 mL of ethyl acetate, and the layers were separated. The organic layer was dried over magnesium sulfate and concentrated in vacuo. Flash chromatography on silica gel using 19:1 v/v, then 9:1 v/v ethyl acetate/petroleum ether as the eluant afforded 3.30 g (56%) of the title compound as a solid: ^{1}H NMR 1.40 (s, 9H), 5.38 (d, 1H), 5.90 (d, 1H), 6.80 (d, 1H), 7.39 (m, 5H), 7.70 (s, 1H), 7.84 (s, 3H).

EXAMPLE 10

1-Phenyl-2-hydroxy-4-(3,5-bis(trifluoromethyl) phenyl)-but-3-enamine•HCl

A solution of 1.00 g (2.1 mmol) of N-t-butoxycarbonyl-1-phenyl-2-oxo-4-(3,5-bis(trifluoromethyl)phenyl)-but-3-enamine (Example 8) in 30 mL of methanol at 0° C. was treated with 241 mg (6.3 mmol) of sodium borohydride. After 30 min, the reaction was quenched with 50 mL of water and concentrated in vacuo to remove the methanol. The mixture was partitioned between 100 mL of ethyl acetate and 50 mL of water and the layers were separated. The organic layer was dried over magnesium sulfate and concentrated in vacuo. Crystallization from ether/hexanes afforded 680 mg (68%) of the title compound as a 5:1 mixture of diastereomers (each protected as the t-butylcarbamate): ^{1}H NMR (* indicates the resonances of the minor diastereomer) 1.40 (s, 9H), 4.60 (dd, 1H), 4.90 (br s, 1H), 5.20 (br d, 1H), 6.30 (dd, 1H), 6.40 (dd, 1H*), 6.70 (dd, 1H), 6.80 (dd, 1H*), 7.40 (m, 5H), 7.80 (m, 3H).

A solution of BOC-protected title compound in methanol (saturated with HCl) was allowed to stand for 72 h. The

solution was concentrated in vacuo. Recrystallization of the resulting solid from ether/hexane afforded 500 mg (80%) of the title compound•HCl as a solid: ^{1}H NMR 4.20 (br s, 1H), 4.40 (d, 1H), 6.20 (dd, 1H), 6.60 (dd, 1H), 7.30 (m 5H), 7.80 (m, 3H).

The title compound•HCl was dissolved in ethyl acetate and 1N aqueous sodium hydroxide solution. The layers were separated; the organic layer was dried over magnesium sulfate and concentrated in vacuo to afford the title compound as the free base.

EXAMPLE 11

2-(2-(3,5-Bis(trifluoromethyl)phenyl)ethenyl)-3-phenyl-5-oxo-morpholine

A solution of 1.95 g (5.2 mmol) of 1-phenyl-2-hydroxy-4-(3,5-bis(trifluoromethyl)phenyl)-but-3-enamine (Example 10) in 20 mL of toluene was added to a suspension of 250 mg (6.2 mmol, 60% dispersion in mineral oil) of sodium hydride in 30 mL of toluene and the resulting mixture was stirred at rt for 15 min. A solution of 0.60 mL (1.15 mol) of ethyl chloroacetate in 5 mL of toluene was slowly added and the resulting mixture was heated at reflux for 3 h. The reaction was cooled, quenched with 50 mL of saturated aqueous ammonium chloride solution, diluted with 50 mL of ethyl acetate and the layers were separated. The organic layer was dried over magnesium sulfate and concentrated in vacuo. Flash chromatography using ethyl acetate/hexanes (4:1 v/v, then 3:1 v/v, then 1:1 v/v) then ethyl acetate as the eluant afforded 300 mg of trans-title compound and 800 mg of cis-title compound (55% total), both as solids. For the cis-isomer: ^{1}H NMR 1.20–1.40 (m, 1H), 1.50–1.62 (m, 1H), 2.60–2.98 (m, 2H), 3.86 (dt, 1H), 4.24 (d, 1H), 4.34 (dd, 1H), 4.45 (d, 1H), 6.40 (br s, 1H), 7.24 (m, 2H), 7.40 (m, 3H), 7.50 (s, 2H), 7.70 (s, 1H).

EXAMPLE 12

3-Phenyl-2-(2-(3.5-bis(trifluoromethyl)phenyl)ethyl)-morpholine

A solution of 95 mg (0.23 mmol) of 2-(2-(3,5-bis(trifluoromethyl)phenyl)ethenyl)-3-phenyl-5-oxo-morpholine (Example 11) in 10 mL of 1:1 v/v ethanol/ethyl acetate was treated with 10 mg of palladium hydroxide and the resulting mixture was stirred under an atmosphere of hydrogen for 2 h. The catalyst was faltered and the filtrate was concentrated in vacuo. The crude product was used directly without further purification.

A solution of 65 mg of the crude morpholinone was dissolved in 10 mL of tetrahydrofuran was treated with 0.84 mL of 1M borane•tetrahydrofuran complex solution in tetrahydrofuran and the resulting solution was heated at reflux for 16 h. The reaction was quenched by adding 10 mL of methanol and 70 mg of potassium carbonate and heating the resulting mixture at reflux for 3 h. All volatiles were removed in vacuo and the residue was partitioned between 20 mL of ethyl acetate and 10 mL of saturated ammonium chloride solution. The organic layer was separated, dried over sodium carbonate, and concentrated in vacuo. The residue was dissolved in saturated HCl in methanol and concentrated in vacuo. The residue was triturated with ether; the resulting solid was filtered and dried to afford 32 mg (46%) of the title compound•HCl, mp 114°–116° C.: ^{1}H NMR 1.42 (m, 1H), 1.66–1.84 (m, 1H), 2.70–2.94 (m, 2H), 3.00 (m, 1H), 3.30–3.46 (m, 1H), 3.80–3.94 (m, 2H), 4.10 (m, 1H), 4.20 (d, 1H), 7.40 (m, 3H), 7.64 (m, 5H); CI-MS 402$(M+1)^+$.

EXAMPLE 13

N-Benzyl-(S)-phenylglycine

A solution of 1.51 g (10.0 mmol) of (S)-phenylglycine in 5 mL of 2N aqueous sodium hydroxide solution was treated with 1.0 mL (10.0 mmol) of benzaldehyde and stirred at room temperature for 20 minutes. The solution was diluted with 5 mL of methanol, cooled to 0° C., and carefully treated with 200 mg (5.3 mmol) of sodium borohydride. The cooling bath was removed and the reaction mixture was stirred at room temperature for 1.5 hours. The reaction was diluted with 20 mL of water and extracted with 2×25 mL of methylene chloride. The aqueous layer was acidified with concentrated hydrochloric acid to pH 6 and the solid that precipitated was filtered, washed with 50 mL of water, 50 mL of 1:1 v/v methanol/ethyl ether and 50 mL of ether, and dried to afford 1.83 g (76%) of product, mp 230°–232° C.

Analysis Calcd for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.17; H, 6.19; N, 5.86.

EXAMPLE 14

3-(S)-Phenyl-4-benzyl-2-morpholinone

A mixture of 4.00 g (16.6 mmol) of N-benzyl-(S)-phenylglycine (from Example 13), 5.00 g (36.0 mmol) of potassium carbonate, 10.0 mL of 1,2-dibromoethane and 25 mL of N,N-dimethylformamide was stirred at 100° C. for 20 hours. The mixture was cooled and partitioned between 200 mL of ethyl ether and 100 mL of water. The layers were separated and the organic layer was washed with 3×50 mL of water, dried over magnesium sulfate and concentrated in vacuo. The residue was purified by flash chromatography on 125 g of silica gel eluting with 9:1 v/v, then 4:1 v/v hexanes/ethyl ether to afford 2.41 g (54%) of the product as a solid, mp 98°–100° C.

Mass Spectrum (FAB): m/Z 268 (M+H, 100%).

^{1}H NMR ($CDCl_3$, 200 MHz, ppm): δ 2.54–2.68 (m, 1H), 2.96 (dt, J=12.8, 2.8, 1H), 3.14 (d, J=13.3, 1H), 3.75 (d, J=13.3, 1H), 4.23 (s, 1H), 4.29–4.37 (m, 1H), 4.53 (dt, J=3.2, 11.0), 7.20–7.56 (m, 10H).

Analysis Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.06; H, 6.40; N, 5.78.

EXAMPLE 15

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenylmorpholine

Step A: 3,5-Bis(trifluoromethyl)benzyl alcohol, trifluoromethanesulfonate ester

A solution of 1.00 g (4.1 mmole) of 3,5-bis(trifluoromethyl)benzyl alcohol and 1.05 g (5.12 mmole) of 2,6-di-t-butyl-4-methylpyridine in 45 mL of dry carbon tetrachloride under a nitrogen atmosphere was treated with 0.74 mL (4.38 mmole) of trifluoromethanesulfonic anhydride at room temperature. A white precipitate formed shortly after the addition of the anhydride. After 90 min, the slurry was filtered under nitrogen with a Schlenk filter, and the filtrate was concentrated in vacuo. The residue, which was a two-phase oil, was dissolved under nitrogen in 10 mL of dry toluene. The resulting clear solution was used immediately in Step B below.

Step B: 4-Benzyl-2-(S)-(3,5-bis(trifluoromethyl) benz-yloxy)-3-(S)-phenylmorpholine

A solution of 0.500 g (1.87 mmole) of N-benzyl-3-(S)-phenylmorpholin-2-one (from Example 14) in 10 mL of dry

THF was cooled to −75° C. under nitrogen and was treated dropwise with 2.06 mL (2.06 mmole) of a 1M solution of lithium tri(sec-butyl)-borohydride (L-Selectride®) in THF. After stirring the solution at −75° C. for 30 min, a solution of 3,5-bis(trifluoromethyl)benzyl alcohol, trifluoromethanesulfonate ester in toluene was added by cannula so that the internal temperature was maintained below −60° C. The resulting solution was stirred at −75° C. for 1 hr and then between −38° C. and −50° C. for 2 hr. The solution was then poured into a mixture of 25 mL of ethyl acetate and 20 mL of saturated aqueous sodium bicarbonate, and the layers were separated. The aqueous phase was extracted with 2×30 mL of ethyl acetate, the combined organic layers were dried over sodium sulfate, the mixture was filtered and the filtrate concentrated in vacuo. The residue was purified by flash chromatography on 130 g of silica eluting with 2 L of 100:5 hexanes:ethyl acetate to give 0.68 g (73%) of an oil, which by ^{1}H NMR is a 20:1 mixture of cis:trans morpholines.

^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ major (cis) isomer: 2.37 (td, J=12, 3.6, 1H), 2.86 (app t, J=13, 2H), 3.57 (d, J=2.6, 1H), 3.63 (dq, J=11.3, 1.6, 1H), 3.89 (d, J=13.3, 1H), 4.12 (td, J=11.6, 2.4, 1H), 4.40 (d, J=13.6, 1H), 4.69 (d, J=2.9, 1H), 4.77 (d, J=13.6), 7.2–7.4 (m, 8H), 7.43 (s, 2H), 7.55 (br d, 2H), 7.69 (s, 1H).

Step C: 2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenylmorpholine

A mixture of 0.68 g (1.37 mmole) of 4-benzyl-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenylmorpholine and 280 mg of 10% Pd/C in 36 mL of 97:3 ethanol:water was stirred under one atmosphere of hydrogen for 15 hr. The mixture was filtered through Celite, the filter cake was washed generously with ethanol, and the filtrated was concentrated in vacuo. The residue was purified by flash chromatography on 68 g of silica eluting with 1 L of 33:67 hexanes:diethyl ether, then 1 L of 25:75 hexanes:diethyl ether to give 0.443 g (80%) of an oil, which by ^{1}H NMR was pure cis morpholine.

^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 1.8 (br s, 1H), 3.10 (dd, J=12.5, 2.9, 1H), 3.24 (td, J=12.2, 3.6, 1H), 3.62 (dd, J=11.3, 2.5, 1H), 4.04 (td, J=11.7, 3, 1H), 4.11 (d, J=2.4, 1H), 4.49 (d, J=13.5, 1H), 4.74 (d, J=2.5, 1H), 4.80 (d, J=13.3, 1H), 7.25–7.40 (m, 5H), 7.40 (s, 2H), 7.68 (s, 1H).

Analysis Calcd for $C_{19}H_{17}F_6NO_2$: C, 56.30; H, 4.23; N, 3.46; F, 28.12. Found: C, 56.20; H, 4.29; N, 3.34; F, 27.94.

EXAMPLE 16

2(R)-3,5-Bis(trifluoromethyl)benzyloxy)-3(R)-phenyl-morpholine

The title compound was prepared from (R)-phenylglycine employing the procedures of Examples 13, 14 and 15.

EXAMPLE 17

4-(3-(1,2,4-Triazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenylmorpholine

Step A: N-Formyl-2-chloroacetamidrazone

A solution of 5 g (66.2 mmole) of chloroacetonitrile in 30 mL of dry methanol was cooled to 0° C. under nitrogen and was treated with 0.1 g (1.8 mmole) of sodium methoxide. The mixture was allowed to warm to room temperature and was stirred for 30 min, and 0.106 mL (1.8 mmole) of acetic acid was added. To the resulting mixture was then added 3.9 g (64.9 mmole) of formic hydrazide, and the material was stirred for 30 min. The reaction mixture was concentrated in vacuo to a solid, and was used as such in Step B below.

Step B: 4-(3-(1,2,4-Triazolo)methyl)-2-(S)-(3,5-bis-(trifluoromethyl)benzyloxy)-3-(S)-phenyl-morpholine

A solution of 0.295 g (0.73 mmole) of 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenylmorpholine (from Example 15) in 10 mL of dry DMF was treated with 0.302 g (2.18 mmole) of anhydrous potassium carbonate and then 0.168 g (1.24 mmole) of N-formyl-2-chloroacetamidrazone (from Example 17, Step A) and the suspension was stirred at 60° C. for 4 hr. The mixture was then heated to 120° C. for 4.5 hr. After cooling, the reaction was diluted with 80 mL of ethyl acetate and the organic layer was washed with 3×20 mL of water. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography on 67 g of silica eluting with 1.5 L of 100:2 methylene chloride:methanol to give 0.22 g of a yellow solid, which was recrystallized from hexanes/methylene chloride to give 0.213 g (60%) of a white crystalline solid, mp 134°–135° C.

Mass Spectrum (FAB): m/Z 487 (M+H, 100%), 259 (35%), 243 (65%), 227 (40%), 174 (25%).

^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 2.67 (td, J=11.9, 3.4, 1H), 2.90 (br d, J=11.7, 1H), 3.43 (d, J=15.2, 1H), 3.66 (app dd, J=13, 1.9, 2H), 3.88 (d, J=15.1, 1H), 4.17 (td, J=11.7, 2.3, 1H), 4.42 (d, J=13.5, 1H), 4.69 (d, J=2.6, 1H), 4.77 (d, J=13.5, 1H), 7.30–7.50 (m, 7H), 7.70 (s, 1H), 7.94 (s, 1H).

EXAMPLE 18

4-(3-(5-Oxo-1H,4H-1,2,4-triazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenylmorpholine

Step A: N-Methylcarboxy-2-chloroacetamidrazone

A solution of 5.0 g (66.2 mmol) of chloroacetonitrile in 35 mL of dry methanol was cooled to 0° C. and was treated with 0.105 g (1.9 mmol) of sodium methoxide. The ice-bath was removed and the mixture was alowed to stir at room temperature for 30 minutes. To the reaction was then added 0.110 mL (1.9 mmol) of acetic acid and then 5.8 g (64.9 mmol) of methyl hydrazinecarboxylate. After stirring 30 minutes at room temperature, the suspension was concentrated in vacuo, and placed on the high-vac line overnight, to give 10.5 g (98%) of a yellow powder, which was employed in Step C below.

^{1}H NMR (CD_3OD, 400 MHz, ppm): δ 3.71 (s, 3H), 4.06 (s, 2H).

Step B: 4-(2-(N-Methylcarboxy-acetamidrazono)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenylmorpholine

A solution of 2.30 g (5.7 mmol) of 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenylmorpholine (from Example 15), 1.13 g (6.8 mmol) of N-methylcarboxy-2-chloroacetamidrazone (from Step A), and 1.50 mL (8.6 mmol) N,N-diisopropylethylamine in 25 mL of acetonitrile was stirred at room temperature for 20 hours. The product, which had preciptated, was filtered, washed with 5 mL of ice cold acetonitrile and dried to give 1.83 g of a white solid. The filtrate was concentrated in vacuo and the residue was partitioned between 50 mL of methylene chloride and 20 mL of water. The layers were separated and the organic layer was dried over magnesium sulfate. The aqueous layer was

extracted with 50 mL of methylene chloride; the extract was dried, combined with the original organic layer, and the combined organics were concentrated in vacuo. The residue was purified by flash chromatography on 30 g of silica gel eluting with 50:1:0.1 v/v/v methylene chloride/methanol/ammonium hydroxide to afford an additional 1.09 g of product (96% total).

Mass Spectrum (FAB): m/Z 535 (M+H, 100%), 462 (16%), 291 (30%), 226 (35%), 173 (25%).

^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 2.53 (dt, J=3.5, 12.2, 1H), 2.59 (d, J=14.6, 1H), 2.94 (d, J=11.8, 1H), 3.37 (d, J=14.6, 1H), 3.58 (d, J=2.8), 1H), 3.62–3.72 (m, 1H), 3.75 (s, 3H), 4.16 (dt, J=2.2, 11.8, 1H), 4.44 (d, J=13.2, 1H), 4.70 (d, J=2.8, 1H), 4.79 (d, J=13.2), 5.55 (br s, 2H), 7.30–7.46 (m, 7H), 7.72 (s, 1H).

Step C: 2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-3-(S)-phenylmorpholine

A solution of 2.89 g (5.4 mmol) of 4-(2-(N-methylcarboxyacetamidrazono)-2-(S)-(3,5-bis(trifluoromethyl) benzyloxy)-3-(S)-phenylmorpholine (from Step B) in 36 mL of xylenes was heated at reflux for 1.5 hours. The solution was cooled and concentrated in vacuo. The residue was taken up in 50 mL of 3:1 v/v hexanes/ethyl acetate which caused crystallization of the product. The product was filtered and dried to afford 1.85 g of a solid. Recrystallization of the solid from 30 mL of 4:1 v/v hexanes/ethyl acetate afforded 1.19 g of pure product as a white solid, mp=156°–157° C. All of the crystallization liquors were combined and concentrated in vacuo. The residue was purified by flash chromatography on 30 g of silica gel eluting with 50:1:0.1 v/v/v methylene chloride/methanol/ammonium hydroxide to afford an additional 0.69 g of a solid. Three recrystallizations from 20 mL of 4:1 v/v hexanes/ethyl acetate afforded an additional 0.39 g of pure product as a white solid (58% total).

Mass Spectrum (FAB): m/Z 503 (M+H), 259 (55%), 226 (40%), 160 (30%).

^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 2.57 (app t, J=9.6, 1H), 2.87–2.97 (m, 2H), 3.58–3.71 (m, 3H), 4.18 (app t, J=10.4, 1H), 4.46 (d, J=13.6), 4.68 (d, J=2.8, 1H), 4.85 (d, J=13.6, 1H), 7.30–7.45 (m, 7H), 7.64 (s, 1H), 10.40 (br s, 1H), 10.73 (br s, 1H).

EXAMPLE 19

N-(2-(R)-Hydroxypropyl)-phenylglycinal, 3,5-bis(tri-fluoromethyl)benzyl acetal

A mixture of 1.00 g (1.5 mmol) of (±)-a-bromophenylacetaldehyde, 3,5-bis(trifluoromethyl)-benzyl acetal (from Example 12), 1.25 mL of (R)-1-amino-2-propanol, 225 mg (1.5 mmol) of sodium iodide, and 3.75 mL of isopropanol was heated at reflux for 20 h. The solution was cooled and concentrated to ~25% the original volume in vacuo. The concentrated solution was partitioned between 50 mL of ether and 20 mL of 2N aqueous sodium hydroxide solution and the layers were separated. The organic layer was washed with 20 mL of saturated aqueous sodium chloride solution, dried over magnesium sulfate and concentrated in vacuo. Flash chromatography on 50 g of silica gel using 65:35 v/v ether/hexane as the eluant afforded 948 mg (95%) of the product as a 1:1 mixture of inseparable diastereomers.

Mass Spectrum (FAB): m/Z 664 (M+H, 25%), 420 (20%), 226 (100%).

EXAMPLE 20

N-(2-(S)-Hydroxypropyl)-phenylglycinal, 3,5-bis(tri-fluoromethyl)benzyl acetal

Substitution of (S)-1-amino-2-propanol for (R)-1-amino-2-propanol in an experiment identical to the preceding example afforded 940 mg (95%) of the product as a 1:1 mixture of diastereomers.

EXAMPLE 21

N-(2-(R)-Hydroxypropyl)-N-(prop-2-enyl)-(R)-phenyl-glycinal, 3,5-bis(trifluoromethyl)benzyl acetal and N-(2-(R)-Hydroxypropyl)-N-(prop-2-enyl)-(S)-phenyl-glycinal, 3,5-bis(trifluoromethyl) benzyl acetal

A mixture of 933 mg (1.40 mmol) of N-(2-(R)-hydroxypropyl)-phenylglycinal, 3,5-bis(trifluoromethyl)-benzyl acetal (from Example 19), 1 mL of allyl bromide, 600 mg (4.3 mmol) of potassium carbonate, and 5 mL of ethanol was stirred at 60° C. for 20 hours. The mixture was cooled, partitioned between 100 mL of ethyl ether and 25 mL of water and the layers were separated. Flash chromatography on 50 g of silica gel using 20:1 v/v ether/hexanes as the eluant afforded 380 mg of the (R,R)-amino alcohol (R_f=0.72 with 3:2 v/v ether/hexanes as the eluant), 220 mg of the (R,S)-amino alcohol (R_f=0.62 with 3:2 v/v ether/hexanes as the eluant), and 285 mg of a mixture of the disastereomeric amino alcohols.

For the (R,R)-amino alcohol:

Mass Spectrum (FAB): m/Z 704(M+H).

IR (neat) 3476, 2932, 1624, 1454, 1361, 1278, 1175, 1132, 760, 704, 682.

^{1}H NMR ($CDCl_3$, 400 MHz, ppm) 1.12 (d, 3H, J=6.4), 2.19 and 2.62 (dAB q, 2H, J_{AB}=13.0, $J_{2.19}$=2.3, $J_{2.62}$=10.4), 2.97 (dd, 1H, J=14.0, 8.8), 3.25–3.30 (m, 1H), 3.76 (s, 1H), 3.77–3.85 (m, 1H), 4.21 (d, 1H, J=8.8), 4.49 and 4.55 (AB q, 2H, J=12.4), 4.86 and 4.92 (AB q, 2H, J=12.4), 5.27–5.33 (m, 2H), 5.39 (d, 1H, J=8.8), 5.79–5.89 (m, 1H), 7.21–7.26 (m, 4H), 7.35-7.40 (m, 3H), 7.67 (s, 1H), 7.81 (s, 1H), 7.85 (s, 2H).

Analysis Calcd for $C_{32}H_{29}F_{12}NO_3$: C, 54.63; H, 4.15; N, 1.99; F, 32.41. Found: C, 54.72; H, 3.94; N, 1.95; F, 32.17.

For the (R,S)-amino alcohol:

Mass Spectrum (FAB): m/Z 704(M+1).

IR (neat) 3451, 2931, 1624, 1454, 1362, 1277, 704, 683.

^{1}H NMR ($CDCl_3$, 400 MHz, ppm) 1.09 (d, 3H, J=6.0), 2.48 and 2.71 (dAB q, 2H, J_{AB}=13.2, $J_{2.48}$=9.6, $J_{2.62}$=3.6), 3.05 (dd, 1H, J=14.4, 6.8), 3.34–3.39 (m, 1H), 3.35 (s, 1H), 3.76–3.81 (m, 1H), 4.21 (d, 1H, J=8.4), 4.50 and 4.54 (AB q, 2H, J=12.8), 4.86 and 4.96 (AB q, 2H, J=12.4), 5.10–5.17 (m, 2H), 5.39 (d, 1H, J=8.4), 5.68–5.78 (m, 1H), 7.23–7.32 (m, 4H), 7.34–7.39 (m, 3H), 7.69 (s, 1H), 7.83 (s, 1H), 7.86 (s, 2H).

Analysis Calcd for $C_{32}H_{29}F_{12}NO_3$: C, 54.63; H, 4.15; N, 1.99; F, 32.41. Found: C, 54.80; H, 4.16; N, 1.90; F, 32.36.

EXAMPLE 22

N-(2-(S)-Hydroxypropyl)-N-(prop-2-enyl)-(S)-phenyl-glycinal, 3,5-bis(trifluoromethyl)benzyl acetal and N-(2-(S)-Hydroxypropyl)-N-(prop-2-enyl)-(R)-phenyl-glycinal, 3,5-bis(trifluoromethyl) benzyl acetal

Substitution of 880 mg (1.33 mmol) of N-(2-(S)-hydroxypropyl)-phenylglycinal, 3,5-bis(trifluoro-methyl)

benzyl acetal (Example 20) for the N-(2-(R)-hydroxypropyl)-phenylglycinal, 3,5-bis(trifluoromethyl)benzyl acetal in the procedures of the preceding example afforded 281 mg of the (S,S)-amino alcohol (R_f=0.72 with 3:2 v/v ether/hexanes as the eluant), 367 mg of the (S,R)-amino alcohol (R_f=0.62 with 3:2 v/v ether/hexanes as the eluant), and 197 mg of a mixture of the disastereomeric amino alcohols.

EXAMPLE 23

2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-6-(R)-methyl morpholine and 2-(S)-(3,5-Bis-(trifluoromethyl)benzyloxy)-3-(R)-phenyl-6-(R)-methyl morpholine

Step A: 2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-4-(2-propenyl)-6-(R)-methyl morpholine and 2-(S)-(3,5-bis(trifluoro-methyl)-benzyloxy)-3-(R)-phenyl-4-(2-propenyl)-6-(R)-methyl morpholine

A solution of 355 mg (0.50 mmol) of N-(2-(R)-hydroxypropyl)-N-(2-propenyl)-(R)-phenylglycinal, 3,5-bis (trifluoromethyl)benzyl acetal (from Example 21) and 285 mg (1.5 mmol) of p-tolensulfonic acid monohydrate in 5 mL of toluene was heated at reflux for 40 min. The solution was cooled and partitioned between 40 mL of ether and 15 mL of saturated aqueous sodium bicarbonate solution. The layers were separated; the organic layer was washed with 10 mL of saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. Flash chromatography on 10 g of silica gel using 19:1 v/v hexanes/ether as the eluant afforded 122 mg of (2R,3R,6R) product (R_f=0.53 with 4:1 v/v hexanes/ether as the eluant) and 62 mg of the (2S,3R,6R) product (R_f=0.23 with 4:1 v/v hexanes/ether as the eluant).

For the (2R,3R,6R) product:

Mass Spectrum (FAB): m/Z 460 (M+H, 65%)

^{1}H NMR ($CDCl_3$, 400 MHz, ppm) 1.35 (d, 3H, J=6.4), 2.53 and 2.63 (dAB q, 2H, J_{AB}=12.0, $J_{2.53}$=3.2, $J_{2.63}$=6.8), 2.83–2.96 (m, 2H), 3.60 (d, 1H, J=4.0), 4.27–4.32 (m, 1H), 4.57 and 4.84 (AB q, 2H, J=13.2), 4.87 (d, 1H, J=4.0), 5.08–5.13 (m, 2H), 5.76–5.86 (m, 1H), 7.31–7.37 (m, 3H), 7.50–7.52 (m, 2H), 7.58 (s, 2H), 7.71 (s, 1H).

For the (2S,3R,6R) product:

Mass Spectrum (FAB): m/Z 460 (M+H, 65%)

^{1}H NMR ($CDCl_3$, 400 MHz, ppm) 1.37 (d, 3H, J=6.8), 2.48–2.50 (m, 2H), 2.74 and 3.01 (dtAB q, 2H, J=6.4, 1.2, 12.4) 3.84 (d, 1H, J=3.6), 3.92–3.99 (m, 1H), 4.70 and 4.93 (AB q, 2H, J=13.6), 4.97 (d, 1H, J=3.6), 5.08–5.14 (m, 2H), 5.74–5.84 (m, 1H), 7.28–7.36 (m, 3H), 7.43–7.46 (m, 2H), 7.64 (s, 2H), 7.75 (s, 1H).

Step B: 2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-6-(R)-methyl morpholine

A solution of 115 mg (0.25 mmol) of the 2-(R)-(3,5-bis (trifluoromethyl)benzyloxy)-3-(R)-phenyl-4-(2-propenyl)-6-(R)-methyl morpholine (from Example 23, Step A) and 230 mg (0.25 mmol) of tris(triphenylphosphine)rhodium chloride in 15 mL of 4:1 v/v acetonitrile/water was heated at reflux for 30 min. The reaction was cooled and partitioned between 50 mL of ethyl acetate and 15 mL of water. The layers were separated and the organic layer was dried over magnesium sulfate. The aqueous layer was extracted with 2×25 mL of ethyl acetate; the extracts were dried and combined with the original organic layer. The combined organics were concentrated in vacuo. The residue was filtered through a pad of silica gel (~20 g) using 2:1 v/v ether/hexanes as the solvent. The filtrate was concentrated; flash chromatography on 5 g of silica gel using 17:3 v/v hexanes/ether as the eluant afforded 67 mg (64%) of 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-6-(R)-methyl morpholine as an oil.

Mass Spectrum (FAB): m/Z 420 (M+H, 90%)

^{1}H NMR ($CDCl_3$, 400 MHz, ppm) 1.21 (d, 3H, J=6.4), 2.02 (br s, 1H), 2.67 and 2.77 (dAB q, 2H, J_{AB}=13.2, $J_{2.67}$=8.8, $J_{2.77}$=3.2), 3.89 (d, 1H, J=2.4), 4.07–4.15 (m, 1H), 4.68 and 4.90 (AB q, 2H, J=12.8), 5.03 (d, 1H, J=2.4), 7.28–7.38 (m, 3H), 7.51–7.53 (m, 2H), 7.77 (s, 2H), 7.79 (s, 1H).

Step C: 2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-6-(R)-methyl morpholine

A similar reaction was carried out using 55 mg (0.12 mmol) of 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-4-(2-propenyl)-6-(R)-methyl morpholine (from Example 23, Step A) and 111 mg (0.12 mmol) of tris (triphenylphosphine)rhodium chloride in 12 mL of 4:1 v/v acetonitrile/water. Flash chromatography on 4 g of silica gel using 50:1 v/v methylene chloride/acetonitrile as the eluant afforded 14 mg (28%) of 2-(S)-(3,5-bis(trifluoromethyl)-benzyloxy)-3-(R)-phenyl-6-(R)-methyl morpholine as an oil.

Mass Spectrum (FAB): m/Z 420 (M+H, 90%)

^{1}H NMR ($CDCl_3$, 400 MHz, ppm) 1.39 (d, 3H, J=6.8), 1.92 (br s, 1H), 2.84 and 2.95 (dAB q, 2H, J_{AB}=12.8, $J_{2.84}$=6.4, $J_{2.95}$=3.6), 3.93–4.00 (m, 1H), 4.07 (d, 1H, J=2.8), 4.68 and 4.95 (AB q, 2H, J=13.2), 4.93 (d, 1H, J=2.8), 7.28–7.37 (m, 3H), 7.48–7.52 (m, 2H), 7.55 (s, 2H), 7.72 (s, 1H).

EXAMPLE 24

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-6-(S)-methyl morpholine and 2-(R)-(3,5-Bis-(trifluoromethyl)benzyloxy)-3-(S)-phenyl-6-(S)-methyl morpholine

Substitution of 350 mg of N-(2-(S)-hydroxy-propyl)-N-(2-propenyl)-(S)-phenylglycinal, 3,5-bis-(trifluoromethyl) benzyl acetal (from Example 22) for N-(2-(R)-hydroxypropyl)-N-(2-propenyl)-(R)-phenyl-glycinal, 3,5-bis(trifluoromethyl)benzyl acetal in an experiment similar to the preceding example afforded 50 mg of 2-(S)-(3,5-bis (trifluoromethhyl)benzyloxy)-3-(S)-phenyl-6-(S)-methyl morpholine and 14 mg of 2-(S)-(3,5-bis(trifluoromethyl) benzyloxy)-3-(S)-phenyl-6-(S)-methyl morpholine.

EXAMPLE 25

2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-6-(R)-methyl morpholine and 2-(S)-(3,5-Bis-(trifluoromethyl)benzyloxy)-3-(S)-phenyl-6-(R)-methyl morpholine

Step A: 2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-4-(2-propenyl)-6-(R)-methyl morpholine and 2-(S)-(3,5-bis(trifluoro-methyl)-benzyloxy)-3-(S)-phenyl-4-(2-propenyl)-6-(R)-methyl morpholine

The title compounds were prepared in a manner similar to Example 23, Step A. Cyclization of 300 mg (0.43 mmol)

N-(2-(R)-hydroxypropyl)-N-(prop-2-enyl)-(S)-phenylglycinal, 3,5-bis(trifluoromethyl)benzyl acetal (from Example 23) was effected using 246 mg (1.29 mmol) of p-toluenesulfonic acid monohydrate and 5 mL of toluene. Flash chromatography on 8 g of silica gel using 20:1 v/v hexanes/ether as the eluant afforded 149 mg (75%) of the products as inseparable diastereomers.

Mass Spectrum (FAB): m/Z 460 (M+H, 65%).

Step B: 2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-6-(R)-methyl morpholine and 2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-6-(R)-methyl morpholine

A solution of 150 mg (0.33 mmol) of 2-(R)-(3,5-bis (trifluoromethyl)benzyloxy)-3-(S)-phenyl-4-(2-propenyl)-6-(R)-methyl morpholine and 2-(S)-(3,5-bis-(trifluoromethyl)-benzyloxy)-3-(S)-phenyl-4-(2-propenyl)-6-(R)-methyl morpholine (from Example 25, Step A) and 318 mg (0.32 mmol) of tris(triphenyl-phosphine)-rhodium chloride in 20 mL of 4:1 v/v acetonitrile/water was heated at reflux for 1 h. Flash chromatography on 5 g of silica gel using 9:1 v/v hexanes/ether as the eluant afforded 35 mg of the products as a mixture and 26 mg of 2-(R)-(3,5-bis-(trifluoromethyl)benzyloxy)-3-(S)-phenyl-6-(R)-methyl morpholine (R_f=0.22 with 3:2 v/v hexanes/ether as the eluant). Chromatography of the mixture on 5 g of silica gel using 20:1 v/v afforded 14 mg of 2-(S)-(3,5-bis (trifluoromethyl)benzyloxy)-3-(S)-phenyl-6-(R)-methyl morpholine (R_f=0.14 with 3:2 v/v hexanes/ether as the eluant) and 17 mg of 2-(R)-(3,5-bis(trifluoromethyl) benzyloxy)-3-(S)-phenyl-6-(R)-methyl morpholine (41% total yield).

For the (2R,3S,6R) product:

Mass Spectrum (FAB): m/Z 420 (M+H, 90%)

^{1}H NMR ($CDCl_3$, 400 Mhz, ppm) 1.30 (d, 3H, J=6.4), 1.74 (br s, 1H), 2.73 and 2.98 (dAB q, 2H, J_{AB}=11.6, $J_{2,73}$=10.0, $J_{2,98}$=2.4), 3.65 (d, 1H, J=7.2), 3.89–3.94 (m, 1H), 4.45 (d, 1H, J=7.2), 4.53 and 4.90 (AB q, 2H, J=13.2), 7.28–7.38 (m, 3H), 7.41–7.43 (m, 2H), 7.45 (s, 2H), 7.70 (s, 1H).

For the (2S,3S,6R) product:

Mass Spectrum (FAB): m/Z 420 (M+H, 90%)

^{1}H NMR ($CDCl_3$, 400 Mhz, ppm) 1.20 (d, 3H, J=6.4), 2.04 (br s, 1H), 2.84 and 3.15 (dAB q, 2H, J_{AB}=12.8, $J_{2.84}$=10.8, $J_{3.15}$=2.8), 4.08 (d, 1H, J=2.8), 4.08–4.15 (m, 1H), 4.53 and 4.80 (AB q, 2H, J=13.2), 4.79 (d, 1H, J=2.8), 7.28–7.38 (m, 5H), 7.43 (s, 2H), 7.70 (s, 1H).

EXAMPLE 26

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-6-(S)-methyl morpholine and 2-(R)-(3,5-Bis-(trifluoromethyl)benzyloxy)-3-(R)-phenyl-6-(S)-methyl morpholine

Substitution of 250 mg of N-(2-(S)-hydroxy-propyl)-N-(2-propenyl)-(S)-phenylglycinal, 3,5-bis-(trifluoromethyl) benzyl acetal (from Example 22) for N-(2-(R)-hydroxypropyl)-N-(2-propenyl)-(R)-phenyl-glycinal, 3,5-bis(trifluoromethyl)benzyl acetal in an experiment similar to the preceding example afforded 42 mg of 2-(S)-(3,5-bis (trifluoromethyl)benzyloxy)-3-(R)-phenyl-6-(S)-methyl morpholine and 17 mg of 2-(S)-(3,5-bis(trifluoro-methyl) benzyloxy)-3-(R)-phenyl-6-(S)-methyl morpholine.

EXAMPLE 27

2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(R)-methyl morpholine, 2-(S)-(3,5-Bis-(tri-fluoromethyl)benzyloxy)-3-(S)-phenyl-5-(R)-methyl morpholine, 2-(R or S)-(3,5-Bis (trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(R)-methylmorpholine, and 2-(S or R)-(3,5-Bis (trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(R)-methylmorpholine

Execution of the sequence described in Example 19 substituting (R)-2-amino-1-propanol for (R)-1-amino-2-propanol provided a mixture of 55 mg of high R_f material and 56 mg of low R_f material. The high R_f material was processed according to Example 23, Step A above to provide 10 mg of high R_f material (2-(R)-(3,5-Bis(trifluoromethyl) benzyloxy)-3-(S)-phenyl-5-(R)-methyl morpholine and 7 mg of low R_f material (2-(S)-(3,5-Bis(trifluoromethyl) benzyloxy)-3-(S)-phenyl-5-(R)-methyl morpholine. The low R_f material (after being combined with an additional 30 mg of material) was processed according to Example 23, Step A to provide 24 mg of high R_f material (2-(R or S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(R) -methyl-morpholine and 18 mg of low R_f material (2-(S or R)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(R) -methylmorpholine.

2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(R)-methyl morpholine

Mass Spectrum (FAB): m/Z 420 (M+H, 100%), 227 (50%), 192 (75%), 176 (65%).

NMR ($CDCl_3$, 400 MHz, ppm): δ 0.98 (d, 3H, J=6.3 Hz), 3.16–3.20 (m, 1H), 3.43–3.47 (m, 1H), 3.79 (d, 1H, J=7.5 Hz), 3.91 (dd, 1H, J=3.2 &11.5 Hz), 4.51 (d, 2H, J=13.4 Hz), 4.85 (d, 1H, J=13.2 Hz), 7.29–7.45 (m, 7H), 7.67 (s, 1H).

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(R)-methyl morpholine

Mass Spectrum (FAB): m/Z 420 (M+H, 48%), 227 (35%), 192 (39%), 176 (100%).

NMR ($CDCl_3$, 400 MHz, ppm): δ 1.10 (d, 3H, J=6.4 Hz), 3.23–3.26 (m, 1H), 3.56–3.61 (m, 2H), 4.17 (d, 1H, J=2.3 Hz), 4.51 (d, 1H, J=13.7 Hz), 4.71 (d, 1H, J=2.4 Hz), 4.78 (d, 1H, J=13.5 Hz), 7.28–7.39 (m, 7H), 7.68 (s, 1H).

2-(R or S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(R)-methyl morpholine

Mass Spectrum (FAB): m/Z 281 (35%), 221 (55%), 207 (45%), 192 (40%), 147 (100%).

NMR ($CDCl_3$, 400 MHz, ppm): δ 1.13 (d, 3H, J=6.6 Hz), 3.10–3.14 (m, 1H), 3.66 (dd, 1H, J=6.6 & 11.4 Hz), 3.76 (dd, 1H, J=3.5 & 11.2 Hz), 4.04 (d, 1H, J=4.0 Hz), 4.61 (d, 1H, J=13.2 Hz), 4.74 (d, 1H, J=3.9 Hz), 4.89 (d, 1H, 13.2 Hz), 7.26–7.35 (m, 3H), 7.47–7.49 (m, 2H), 7.64 (s, 1H), 7.74 (s, 1H).

2-(R or S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(R)-methyl morpholine

NMR ($CDCl_3$, 400 MHz, ppm): δ 1.36 (d, 3H, J=6.7 Hz), 3.27–3.31 (m, 1H), 3.39 (dd, 1H, J=2.2 & 11.3 Hz), 4.16 (dd, 1H, J=3.2 & 11.0 Hz), 4.37 (d, 1H, J=2.3 Hz), 4.53 (d, 1H, J=13.5 Hz), 4.75 (d, 1H, J=2.5 Hz), 4.81 (d, 1H, 13.6 Hz), 7.26–7.35 (m, 3H), 7.26–7.43 (m, 7H), 7.68 (s, 1H).

EXAMPLE 28

2-(R or S)-(3,5-Bis(trifluoromethyl)-benzyloxy)-3-(S)-phenyl-5-(S)-methylmorpholine, 2-(S or R)-(3,5-(-Bis-(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(S)-methyl-morpholine, and 2-(R)-(3,5-Bis (trifluoromethyl)benzyl-oxy)-3-(R)-phenyl-5-(S)-methylmorpholine

Execution of the sequence described in Example 19 substituting (S)-2-amino-1-propanol for (R)-1-amino-2-

propanol provided a mixture of 78 mg of high R_f material and 70 mg of low R_f material. The high R_f material was processed according to Example 23, Step A above to provide less than 1 mg of high R_f material (2-(R)-(3,5-Bis (trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(S)-methylmorpholine) and 9 mg of low R_f material (2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(S)-methyl morpholine. The low R_f material was processed according to Example 23, Step A to provide 20 mg of high R_f material (2-(R or S)-(3,5-Bis(trifluoromethyl)benzyloxy) -3-(S)-phenyl-5-(S)-methylmorpholine and 14 mg of low R_f material (2-(S or R)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(S)-methylmorpholine.

2-(R or S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(S)-methyl morpholine

Mass Spectrum (FAB): m/Z 420 (M+H, 60%), 227 (68%), 192 (56%), 176 (100%).

NMR ($CDCl_3$, 400 MHz, ppm): δ 1.12 (d, 3H, J=6.6 Hz), 3.09–3.14 (m, 1H), 3.65 (dd, 1H, J=6.6 & 11.0 Hz), 3.75 (dd, 1H, J=3.6 & 11.1 Hz), 4.04 (d, 1H, J=3.9 Hz), 4.61 (d, 1H, J=13.2 Hz), 4.73 (d, 1H, J= 3.9 Hz), 4.89 (d, 1H, 13.2 Hz), 7.28–7.35 (m, 3H), 7.47 (d, 2H, 7.0 Hz), 7.64 (s, 1H), 7.74 (s, 1H).

2-(S or R)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(S)-methyl morpholine

Mass Spectrum (FAB): m/Z 420 (M+H, 50%), 227 (45%), 192 (40%), 176 (100%).

NMR ($CDCl_3$, 400 MHz, ppm): δ0 1.36 (d, 3H, J=6.9 Hz), 3.27–3.29 (m, 1H), 3.39 (dd, 1H, J=2.2 & 11.1 Hz), 4.15 (dd, 1H, J=3.3 & 11.1 Hz), 4.37 (d, 1H, J=2.5 Hz), 4.52 (d, 1H, J=13.3 Hz), 4.75 (d, 1H, J=2.4 Hz), 4.81 (d, 1H, 13.5 Hz), 7.28–7.43 (m, 7H), 7.68 (s, 1H).

2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(S)-methyl morpholine

NMR ($CDCl_3$, 400 MHz, ppm): δ 1.10 (d, 3H, J=6.4 Hz), 3.22–3.25 (m, 1H), 3.55–3.60 (m, 2H), 4.17 (d, 1H, J=2.3 Hz), 4.51 (d, 1H, J=13.5 Hz), 4.71 (d, 1H, J=2.4 Hz), 4.77 (d, 1H, J=13.6 Hz), 7.28–7.38 (m, 7H), 7.67 (s, 1H).

EXAMPLE 29

2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(R)-phenylmorpholine, 2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(R)-phenyl-morpholine, and 2-(R or S)-(3,5-Bis (trifluoromethyl)-benzyloxy)-3-(R)-phenyl-5-(R)-phenylmorpholine

Execution of the sequence described in Example 19 substituting (R)-2-amino-2-phenylethanol for (R)-1-amino-2-propanol provided a mixture of 62 mg of high R_f material and 52 mg of low R_f material. The high R_f material was processed according to Example 23, Step A above to provide 16 mg of high R_f material (2-(R)-(3,5-B is(trifluoromethyl) benzyloxy)-3-(S)-phenyl-5-(R)-phenylmorpholine and 4 mg of low R_f material (2-(S)-(3,5-Bis(trifluoromethyl) benzyloxy)-3-(S)-phenyl-5-(R)-phenylmorpholine. The low R_f material was processed according to Example 23, Step A to provide 4 mg of product (2-(R or S)-(3,5-Bis (trifluoromethyl)benzyl-oxy)-3-(R)-phenyl-5-(R)-phenylmorpholine.

2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(R)-phenylmorpholine

NMR ($CDCl_3$, 400 MHz, ppm): δ 3.62 (t, 1H, J=10.7 & 21.5 Hz), 3.93 (d, 1H, J=7.4 Hz), 3.99 (dd, 1H, J=3.1 & 11.2 Hz), 4.18 (dd, 1H, J=3.0 & 10.2 Hz), 4.46 (d, 1H, J=7.4 Hz), 4.53 (d, 1H, J=13.5 Hz), 4.89 (d, 1H, J=13.3 Hz), 7.28–7.55 (m, 12H), 7.69 (s, 1H).

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(R)-phenylmorpholine

NMR ($CDCl_3$, 400 MHz, ppm): δ 3.67 (dd, 1H, J=3.5 & 11.0 Hz), 3.89 (d, 1H, J=10.8 & 21.6 Hz), 4.25 (dd, 1H, J=3.3 & 11.0 Hz), 4.34 (d, 1H, J=2.2 Hz), 4.52 (d, 1H, J=13.8 Hz), 4.78–4.87 (m, 2H), 7.28–7.51 (m, 12H), 7.69 (s, 1H).

2-(R or S)-(3.5-Bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(R)-phenylmorpholine

NMR ($CDCl_3$, 400 MHz, ppm): δ 4.10–4.25 (m, 2H), 4.30–4.38 (m, 1H), 4.48–4.54 (m, 1H), 4.59–4.66 (m, 1H), 4.86–5.00 (m, 2H), 7.25–7.74 (m, 13H).

EXAMPLE 30

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(S)-phenylmorpholine, 2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(S)-phenyl-morpholine, 2-(R or S)-(3,5-Bis-(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(S)-phenyl-morpholine, and 2-(R or S)-(3,5-Bis (trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(S)-phenylmorpholine

Execution of the sequence described in Example 19 substituting (S)-2-amino-2-phenylethanol for (R)-1-amino-2-propanol provided a mixture of 75 mg of high R_f material and 64 mg of low R_f material. The high R_f material was processed according to Example 23, Step A above to provide 23 mg of high R_f material (2-(S)-(3,5-Bis(trifluoromethyl) benzyloxy)-3-(R)-phenyl-5-(S)-phenylmorpholine [L-740, 930]) and 7 mg of low R_f material (2-(R)-(3,5-Bis (trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(S)-phenylmorpholine. The low R_f material was processed according to Example 23, Step A to provide 26 mg of higher R_f material (2-(R or S)-(3,5-Bis(trifluoromethyl)benzyloxy) -3-(S)-phenyl-5-(S)-phenylmorpholine and 6 mg of lower R_f material (2-(R or S)-(3,5-Bis(trifluoro-methyl)benzyloxy)-3-(S)-phenyl-5-(S)-phenylmorpholine.

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(S)-phenylmorpholine

NMR ($CDCl_3$, 400 MHz, ppm): δ 3.60–3.74 (m, 1H), 3.94 (d, 1H, J=7.6 Hz), 4.00 (dd, 1H, J=3.2 & 11.3 Hz), 4.18–4.21 (m, 1H), 4.50–4.55 (m, 2H,), 4.89 (m, 1H), 7.26–7.55 (m, 12H), 7.69 (s, 1H).

2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(S)-phenylmorpholine

NMR ($CDCl_3$, 400 MHz, ppm): δ 3.68 (dd, 1H, J=3.0 & 11.0 Hz), 3.88–3.94 (m, 1H), 4.26–4.30 (m, 1H), 4.36 (s, 1H), 4.52 (d, 1H, J=13.5 Hz), 4.77–4.86 (m, 2H), 7.27–7.51 (m, 12H), 7.69 (s, 1H).

2-(R or S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(S)-phenylmorpholine

NMR ($CDCl_3$, 400 MHz, ppm): δ 3.93–3.95 (m, 1H), 4.06–4.21 (m, 2H), 4.38–4.42 (m, 1H), 4.59–4.68 (m, 2H), 4.83–4.94 (m, 2H), 7.25–7.81 (m, 13H).

2-(R or S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(S)-phenylmorpholine

NMR ($CDCl_3$, 400 MHz, ppm): δ 3.43–3.59 (m, 2H), 3.82 (d, 1H, J=7.2 Hz), 4.25 (d, 1H, J=12.5 Hz), 4.52–4.63 (m, 3H), 4.80–4.90 (br s, 1H), 7.11–7.81 (m, 13H).

EXAMPLE 31

2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-6-(R)-methyl-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine

According to the procedure given in Example 17, Step B, 98 mg (0.24 mmole) of 2-(S)-(3,5-bis-(trifluoromethyl) benzyloxy)-3-(S)-phenyl-6-(R)-methyl morpholine (from Example 25 above), 38 mg (0.28 mmole) of N-formyl-2-chloroacetamidrazone (from Example 17, Step A above) and 97 mg (0.7 mmole) of anhydrous potassium carbonate gave, after flash chromatography on 28 g of silica eluting with 1 L of 100:4:0.5 methylene chloride:methanol:ammonia water, a light yellow solid which after recrystallization from hexanes/methylene chloride provided 77 mg (66%) of 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-6-(R)-methyl-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl)morpholine as a white powder.

NMR ($CDCl_3$, 400 MHz, ppm): δ 1.17 (d, J=6.3, 3H), 2.29 (t, J=11.1, 1H), 2.92 (d, J=11.1, 1H), 3.42 (d, J=15.3, 1H), 3.58 (s, 1H), 3.88 (d, J=15.4, 1H), 4.20–4.33 (m, 1H), 4.43 (d, 13.5, 1H), 4.71 (d, J=2.4, 1H), 4.74 (d, J=13.3, 1H), 7.30–7.55 (m, 7H), 7.69 (s, 1H), 7.95 (s, 1H).

EXAMPLE 32

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-6-(R)-methyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-3-(S)-phenylmorpholine

A mixture of 96 mg (0.23 mmole) of 2-(S)-(3,5-bis (trifluoromethyl)benzyloxy)-3-(S)-phenyl-6-(R)-methyl morpholine (from Example 25 above), 46 mg (0.28 mmole) of N-methylcarboxy-2-chloroacetamidrazone and 95 mg (0.69 mmole) of anhydrous potassium carbonate in 3 mL of dry DMF was stirred at room temperature for 20 min, at 60° C. for 90 min and then at 120° C. for 2 hr. The mixture was cooled to room temperature, taken up in 15 mL of ethyl acetate and was washed with 3×10 mL of water. The combined aqueous layers were back-extracted with 10 mL of ethyl acetate, the combined organic layers were washed with 10 mL of brine, dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography on 28 g of silica eluting with 1 L of 100:4 methylene chloride:methanol to give 65 mg (55%) of 2-(S)-(3,5-bis(trifluoromethyl)benzyl-oxy)-6-(R)-methyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-3-(S)-phenylmorpholine as a light yellow powder.

NMR ($CDCl_3$, 400 MHz, ppm): δ 1.18 (d, J=6.2, 3H), 2.15 (t, J=11.1, 1H), 2.89 (d, J=14, 2H), 3.49 (d, J=2.2, 1H), 3.61 (d, J=14.4, 1H), 4.20–4.30 (m, 1H), 4.45 (d, J=13.6, 1H), 4.67 (d, J=2.5, 1H), 4.79 (d, J=13.5, 1H), 7.25–7.50 (m, 7H), 7.62 (s, 1H), 10.07 (s, 1H), 10.35 (s, 1H).

EXAMPLE 33

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(R)-phenylmorpholine

Step A: 4-Benzyl-2-(S)-hydroxy-3-(R)-phenylmorpholine

A solution of 3.72 g (13.9 mmol) of 4-benzyl-3-(R)-phenyl-2-morpholinone, prepared from (R)-phenyl-glycine as described in Example 14, in 28 mL of CH_2Cl_2 was cooled in a −78° C. bath under a N_2 atmosphere and 14 mL of a 1.5M solution of DIBAL-H (21 mmol) in toluene were added. After stirring the resulting solution for 0.5 h, it was allowed to warm to −50° C. and mantained at this temperature for 0.5 h. The reaction mixture was quenched by adding 10 mL of aqueous potassium sodium tartarate. The mixture was diluted with CH_2Cl_2 and the layers were separated. The aqueous layer was extracted 3 times with CH_2Cl_2. The CH_2Cl_2 layers were washed with brine, dried over Na_2SO_4 and filtered. Concentration of the filtrate furnished 3.32 g (88%) of 4-benzyl-2-(S)-hydroxy-3-(R)-phenylmorpholine suitable for use in the next step.

NMR ($CDCl_3$) 2.28 (m, 1H), 2.71 (m, 1H), 2.91 (d, J=13 Hz, 1H), 3.09 (d, J=6 Hz, 1H), 3.69 (d, J=13 Hz, 1H), 3.82 (td, J=10 Hz and 2 Hz, 1H), 3.91 (d, J=10 Hz, 1H), 4.73 (t, J=6 Hz, 1H), 7.2–7.52 (m, 10H).

Step B: 4-Benzyl-2-(S)-(3,5-bis(trifluoromethyl)-benzyloxy)-3-(R)phenylmorpholine

To a suspension of 0.592 g (14.8 mmol) of NaH in 30 mL of dry THF at 0° C. was added 3.32 g (12.3 mmol) of 4-benzyl-2-(S)-hydroxy-3-(R)-phenyl-morpholine prepared in step A. After 15 min 0.915 g of tetrabutylammonium iodide (2.47 mmol) and 2.4 mL (13 mmol) of 3,5-bis (trifluoromethyl)benzyl bromide were added. The resulting mixture was stirred at ice-bath temperature for 1 h, then poured into saturated $NaHCO_3$ solution and extracted with ethyl acetate (EtOAc). The organic layers were combined, washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuo and the resiue was chromatographed on a Waters Prep500 HPLC system using 50% EtOAc/Hexane to isolate 3.6 g (59%) of 4-Benzyl-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenylmorpholine.

^1H NMR ($CDCl_3$) 2.3 (td, J=11 Hz and 3Hz, 1H), 2.71 (d, J=11 Hz, 1H), 2.90 (d, J=13 Hz, 1H), 3.22 (d, J=7.3 Hz, 1H), 3.75 (m, 2H), 3.93 (m, 1H), 4.43 (d, J=13 Hz, 1H), 4.45 (d, J=7.3 Hz, 1H), 4.82 (d, J=13 Hz, 1H), 7.19–7.5 (m, 12H), 7.67 (s, 1H).

Step C: 2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(R)-phenylmorpholine

A solution of 3.6 g (7.27 mmol) of 4-benzyl-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenylmorpholine in 100 mL of ethanol and 5 mL of water, containing 0.72 g of 10% Pd/C was hydrogenated on a Parr apparatus for 36 h. The catalyst was filtered and thoroughly washed with EtOAc. The filtrate was concentrated and the residue was partitioned between water and EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography using a gradient of 10–60% EtOAc/hexane to isolate 2.05 g (70%) of 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenylmorpholine.

^1H NMR ($CDCl_3$) 1.92 (br s, 1H), 2.91 (m, 1H), 3.05 (td, J=11 Hz and 3 Hz, 1H), 3.68 (d, J=7 Hz, 1H), 3.81 (td, J=11 Hz and 3 Hz, 1H), 4.01 (m, 1H), 4.44 (d, J=7Hz), 4.5 (d, J=13 Hz, 1H), 4.85 (d, J=13 Hz, 1H), 7.28–7.42 (m, 7H), 7.67 (s, 1H).

EXAMPLE 34

4-(3-(1,2,4-Triazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenylmorpholine

The title compound was prepared by the procedure of Example 17, step B employing the product of Example 33, step C as a starting material.

^1H NMR ($CDCl_3$) 1.75 (br s, 1H), 2.61 (td, J=12 Hz and 2 Hz, 1H), 2.83 (d, J=12 Hz, 1H), 3.33 (d, J=7 Hz, 1H), 3.48

(d, J=15 Hz, 1H), 3.78 (d, J=15 Hz, 1H), 3.85 (m, 1H), 3.99 (m, 1H), 4.44 (d, J=13 Hz, 1H), 4.49 (d, J=7 Hz, 1H), 4.81 (d, J=13 Hz, 1H), 7.23–7.45 (m, 7H), 7.67 (s, 1H), 7.96 (s, 1H).

EXAMPLE 35

4-(3-(5-Oxo-1H,4H-1,2,4-triazolo)methyl)-2-(S)-(3,5-bis-(trifluoromethyl)benzyloxy)-3-(R)-phenylmorpholine

The title compound was prepared by the procedure of Example 18, steps B & C employing the product of Example 33, step C as a starting material.

EXAMPLE 36

4-(2-(Imidazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenylmorpholine

A solution of 101 mg (0.25 mmol) of 2-(S)-(3,5-bis (trifluoromethyl)benzyloxy)-3-(S)-phenylmorpholine (Example 15), 98 mg (1.0 mmol) of imidazole-2-carboxaldehyde, and 5 drops of glacial acetic acid in 3 ml of methanol was treated with 1.5 ml of 1M sodium cyanoborohydride solution in THF. After 16 hr, the reaction was quenched with 5 ml of saturated aqueous sodium bicarbonate solution and partitioned between 40 ml of ethyl acetate and 20 ml of water. The organic layer was separated, dried over magnesium sulfate, and concentrated in vacuo. Flash chromatography on 8 g of silica gel using 0:1:0.1 methylene chloride/methanol/amonium hydroxide as the eluent afforded 54 mg (44% yield) of the title compound as a white solid.

^{1}H NMR ($CDCl_3$) 2.60 (dt, J=3.2 Hz and 12.4 Hz, 1H), 2.85 (d, J=12.4 Hz, 1H), 3.28 (d, J=14.4 Hz, 1H), 3.59 (d, J=2.8 Hz, 1H), 3.66 (dd, J=2.0, 11.6 Hz, 1H), 3.84 (d, J=14.4 Hz, 1H), 3.94 (app s, 2H), 4.14 (dt, J=2.0, 12.0 Hz, 1H), 4.43 (d, J=13.6 Hz, 1H), 4.71 (d, J=2.8 Hz, 1H), 4.78 (d, J=13.6 Hz, 1H), 6.99 (app s, 2H), 7.25–7.48 (m, 6H), 7.72 (s, 1H). Mass spectrum (FAB): m/z 486 (100%, M+H)

EXAMPLE 37

4-(2-(Imidazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenylmorpholine

The title compound was prepared by the procedure of Example 36 employing appropriate starting materials.

^{1}H NMR ($CDCl_3$) 2.53 (td, J=11 Hz and 3 Hz, 1H), 2.74 (d, J=12 Hz, 1H), 3.23 (d, J=7 Hz, 1H), 3.32 (d, J=15 Hz, 1H), 3.66 (d, J=15 Hz, 1H), 3.77 (td, J=11 Hz and 2 Hz, 1H), 3.99 (m, 1H), 4.44 (m, 2H), 4.8 (d, J=13 Hz, 1H), 6.94 (s, 2H), 7.2–7.45 (m, 7H), 7.67 (s, 1H).

EXAMPLE 38

4-(5-(Imidazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenylmorpholine

The title compound was prepared by the procedure of Example 36 employing appropriate starting materials.

^{1}H NMR ($CDCl_3$) 2.47 (td, J=12 Hz and 3 Hz, 1H), 2.83 (d, J=12 Hz, 1H), 3.2 (m, 2H), 3.61 (d, J=14 Hz, 1H), 3.79 (td, J=12 Hz and 2 Hz, 1H), 3.96 (m, 1H), 4.44 (m, 2H), 4.80 (d, J=13 Hz, 1H), 6.81 (s, 1H), 7.28–7.45 (m, 7H), 7.60 (s, 1H), 7.66 (s, 1H).

EXAMPLE 39

4-(Aminocarbonylmethyl)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenylmorpholine

The title compound was prepared by the procedure of Example 15 employing appropriate starting materials.

^{1}H NMR ($CDCl_3$) 2.54 (td, J=11 Hz and 2 Hz, 1H), 2.64 (d, J=17 Hz, 1H), 2.93 (d, J 12 Hz, 1H), 3.14 (d, J=17 Hz, 1H), 3.27 (d, J=7 Hz, 1H), 3.83 (td, J=11 Hz and 2 Hz, 1H), 4.05 (m, 1H), 4.46 (m, 2H), 4.81 (d, J=13 Hz, 1H), 5.62 (br s, 1H), 6.80 (br s, 1H), 7.28–7.32 (m, 7H), 7.67 (s, 1H).

EXAMPLES 40–43

4-(3-(1,2,4-Triazolo)methyl)-2-(3-(tert-butyl)-5-methylbenzyloxy)-3-phenyl-morpholine, 4-(3-(5-Oxo-1H,4H-1,2,4-triazolo)methyl)-2-(3-(tert-butyl)-5-methylbenzyloxy)-3-phenyl-morpholine, 4-(2-(Imidazolo)methyl)-2-(3-(tert-butyl)-5-methylbenzyloxy)-3-phenylmorpholine, 4-(4-(Imidazolo)methyl)-2-(3-(tert-butyl)-5-methylbenxyloxy)-3-phenyl-morpholine

The title compounds are each prepared by the procedures of Examples 15, 17 & 18 employing appropriately substituted starting materials and reagents.

EXAMPLE 44

2-(S)-(3,5-Dichlorobenzyloxy)-3-(S)-phenylmorpholine

Step A: 3,5-Dichlorobenzyl alcohol, trifluoromethanesulfonate ester

A solution of 6.09 g (34.4 mmole) of 3,5-dichlorobenzyl alcohol and 8.48 g (41.3 mmole) of 2,6-di-t-butyl-4-methylpyridine in 280 mL of dry carbon tetrachloride under a nitrogen atmosphere was treated with 5.95 mL (35.4 mmole) of trifluoromethanesulfonic anhydride at room temperature. A white precipitate formed shortly after the addition of the anhydride. After 90 min, the slurry was filtered under nitrogen with a Schlenk filter, and the filtrate was concentrated in vacuo. The residue, which was a two-phase oil, was dissolved under nitrogen in 60 mL of dry toluene. The resulting solution was used immediately in Step B below.

Step B: 4-Benzyl-2-(S)-(3,5-dichlorobenzyloxy)-3-(S)-phenylmorpholine

A solution of 5.11 g (19.1 mmole) of N-benzyl-3-(S)-phenylmorpholin-2-one (from Example 14) in 100 mL of dry THF was cooled to −75° C. under nitrogen and was treated dropwise with 20.5 mL (20.5 mmole) of a 1M solution of lithium tri(sec-butyl)borohydride (L-Selectride®) in THF. After stirring the solution at −75° C. for 30 min, a solution of 3,5-dichlorobenzyl alcohol, trifluoromethanesulfonate ester in toluene (from Example 44, Step A) was added by cannula so that the internal temperature was maintained below −60° C. The resulting solution was stirred between −38° C. and −50° C. for 9 hr, and was then treated with 14 mL of aqueous ammonia and stored at −20° C. for 12 hours. The solution was then poured into a mixture of 50 mL of ethyl acetate and 100 mL of water, and the layers were separated. The aqueous phase was extracted with 2×100 mL of ethyl acetate, each extract was washed with brine, the combined organic layers were dried over sodium sulfate, the mixture was filtered and the filtrate concentrated in vacuo. The residue was purified by flash chromatography on 235 g of silica eluting with 1.5 L of 100:2 hexanes:ethyl acetate, then 1.5 L of 100:3 hexanes:ethyl acetate and then 1.9 L of 100:5 hexanes:ethyl acetate to give 4.4 g (54%) of an oil, which by ^{1}H NMR is a 8:1 mixture of cis:trans morpholines.

Mass Spectrum (FAB): m/Z 430.428.426 (M+H, ~60%), 268 (M—$ArCH_2$, 100%), 252 (M—$ArCH_2O$, 75%), 222 (20%), 159 (45%).

^1H NMR ($CDCl_3$, 400 MHz, ppm): δ major (cis) isomer: 2.32 (td, J=12, 3.6, 1H), 2.84 (app t, J=13, 2H), 3.52 (d, J=2.6, 1H), 3.55 (dq, J=11.3, 1.6, 1H), 3.91 (d, J=13.3, 1H), 4.12 (td, J=11.6, 2.4, 1H), 4.29 (d, J=13.6, 1H), 4.59 (d, J=2.9, 1H), 4.60 (d, J=13.6), 6.70 (s, 2H), 7.13 (t, J=1.9, 1H), 7.2–7.6 (m, 8H), 7.53 (br d, 2H).

Step C: 2-(S)-(3,5-Dichlorobenzyloxy)-3-(S)-phenyl-morpholine

A solution of 0.33 g (0.77 mmole) of 4-benzyl-2-(S)-(3,5-dichlorobenzyloxy)-3-(S)-phenylmorpholine (from Example 44, Step B) and 0.22 g (1.54 mmole) of 1-chloroethyl chloroformate in 4.5 mL of 1,2-dichloroethane was placed in a pressure vial which was lowered into an oil bath which was heated to 110° C. After stirring for 60 hr the solution was cooled and concentrated in vacuo. The residue was dissolved in 7 mL of methanol and the resulting solution was heated at reflux for 30 min. The mixture was cooled and treated with several drops of concentrated aqueous ammonia and the solution was concentrated. The residue was partly purified by flash chromatography on 67 g of silica eluting with 1.5 L of 100:1 methylene chloride:methanol, and the rich cuts were purified by flash chromatography on 32 g of silica eluting with 50:50 hexanes:ethyl acetate and then 50:50:5 hexanes:ethyl acetate:methanol to give 0.051 g (20%) of an oil, which by ^1H NMR was pure cis morpholine.

Mass Spectrum (FAB): m/Z 468,466,464 (max 8%)), 338,340 (M+H, 25%), 178 (20%), 162 (100%), 132 (20%),

^1H NMR ($CDCl_3$, 400 MHz, ppm): δ 1.89 (br s, 1H), 3.08 (dd, J=12.5, 2.9, 1H), 3.23 (td, J=12.2, 3.6, 1H), 3.59 (dd, J=11.3, 2.5, 1H), 4.03 (td, J=11.7, 3, 1H), 4.09 (d, J=2.4, 1H), 4.37 (d, J=13.5, 1H), 4.62 (d, J=13.3, 1H), 4.67 (d, J=2.5, 1H), 6.72 (d, J=1.8, 2H), 7.14 (t, J=1.8, 1H), 7.25–7.40 (m, 5H).

EXAMPLE 45

2-(S)-(3,5-dichlorobenzyloxy)-4-(3-(5-oxo-1,2,4-triazolo)methyl)-3-(S)-phenylmorpholine

Step A: N-Methylcarboxy-2-chloroacetamidrazone

A solution of 5.0 g (66.2 mmol) of chloroacetonitrile in 35 mL of dry methanol was cooled to 0° C. and was treated with 0.105 g (1.9 mmol) of sodium methoxide. The ice-bath was removed and the mixture was alowed to stir at room temperature for 30 minutes. To the reaction was then added 0.110 mL (1.9 mmol) of acetic acid and then 5.8 g (64.9 mmol) of methyl hydrazinecarboxylate. After stirring 30 minutes at room temperature, the suspension was concentrated in vacuo, and placed on the high-vac line overnight, to give 10.5 g (98%) of a yellow powder, a portion of which was employed in Step C below.

Step B: 4-(2-(N-Methylcarboxy-acetamidrazono)-2-(S)-(3,5-dichlorobenzyloxy)-3-(S)-phenylmorpholine

A solution of 0.050 g (0.15 mmol) of 2-(S)-(3,5-dichlorobenzyloxy)-3-(S)-phenylmorpholine (from Example 44, Step C), 0.034 g (0.21 mmol) of N-methyl-carboxy-2-chloroacteamidrazone (from Step A), and 0.044 mL (0.25 mmol) N,N-diisopropylethylamine in 1 mL of acetonitrile was stirred at room temperature for 3 hours. The mixture was partitioned between 20 mL of methylene chloride and 10 mL of water. The layers were separated, the organic layer was dried over sodium sulfate and was then concentrated in vacuo. The residue was purified by flash chromatography on 35 g of silica eluting with 1 L of 50:1: methylene chloride/methanol then 500 mL of 25:1:0.05 methylene chloride:methanol:aqueous ammonia to give 70 mg (~100%) of the product as a white solid.

Mass Spectrum (FAB): m/Z 469 (M+H, 60%), 467 (M+H, 100%),291 (40%), 160 (20%), 158 (25%).

^1H NMR ($CDCl_3$, 400 MHz, ppm): δ 2.48 (td, J=3.5, 12.2, 1H), 2.53 (d, J=14.6, 1H), 2.90 (d, J=11.8, 1H), 3.37 (d, J=14.6, 1H), 3.52 (d, J=2.8), 1H), 3.62 (dm, J=11.4, 1H), 3.75 (s, 3H), 4.14 (td, J=2.2, 11.8, 1H), 4.28 (d, J=13.5, 1H), 4.58 (d, J=13.6), 4.60 (d, J=2.8, 1H), 5.45 (br s, 2H), 6.74 (d, J=1.9, 2H), 7.15 (t, J=1.9, 1H), 7.30–7.46 (m, 6H).

Step C: 2-(S)-(3,5-Dichlorobenzyloxy)-4-(3-(5-oxo-1,2,4-triazolo)methyl)-3-(S)-phenylmorpholine

A solution of 0.069 g (0.15 mmol) of 4-(2-(N-methylcarboxyacetamidrazono)-2-(S)-(3,5-dichlorobenzyloxy)-3-(S)-phenylmorpholine (from Step B) in 6 mL of xylenes was heated at reflux for 2 hours. The solution was cooled and concentrated in vacuo. The residue was purified by flash chromatography on 35 g of silica gel eluting with 500 mL of 50:1:0.1 methylene chloride/methanol/aqueous ammonia then 500 mL of 20:1:0.1 methylene chloride/methanol/aqueous ammonia to give 56 mg (88%) of the product as a white powder.

Mass Spectrum (FAB): m/Z 437 (M+H, 65%), 435 (M+H, 100%), 259 (85%), 161 (55%).

^1H NMR ($CDCl_3$, 400 MHz, ppm): δ 2.53 (t, J=11.7, 3.6, 1H), 2.88 (d,J=11.6, 1H), 2.96 (d, J=14.3, 1H), 3.54 (d, J=2.6, 1H), 3.63 (dd, J=11.6, 1.9, 1H), 3.68 (d, J=14.6, 1H), 4.16 (t, J=11.7, 2.2, 1H), 4.30 (d, J=13.6), 4.58 (d, J=2.7, 1H), 4.67 (d, J=13.6, 1H), 6.65 (d, J=1.8, 2H), 7.07 (t, J=1.9, 1H), 7.29–7.44 (m, 5H), 10.25 (br s, 1H), 10.75 (br s, 1H).

EXAMPLE 46

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-4-(methoxy-carbonylmethyl)-3-(S)-phenylmorpholine

A solution of 300 mg (0.74 mmole) of 2-(S)-(3,5-bis (trifluoromethyl)benzyloxy)-3-(S)-phenyl-morpholine (from Example 15, Step C) and 0.35 mL (2.0 mmole) of DIEA in 5 mL of acetonitrile was treated with 0.19 mL (2.0 mmole) of methyl bromoacetate and the mixture was stirred for 16 hr at room temperature. The solution was then concentrated in vacuo and the residue partitioned between 30 mL of ether and 15 mL of 0.5N aqueous $KHSO_4$. The layers were separated and the organic phase was washed with 10 mL of brine and dried over magnesium sulfate. Following filtration, the organic phase was concentrated in vacuo and the residue purified by flash chromatography on 20 g of silica eluting with 80:20 hexanes:ether to give 351 mg (99%) of the product. $[a]_D$=+147.3° (c=1.6, $CHCl_3$).

Mass Spectrum (FAB): m/Z 478 (M+H, 40%), 477 (65%), 418 (50%), 250 (95%), 234 (90%), 227 (100%).

^1H NMR ($CDCl_3$, 400 MHz, ppm): δ 3.02 (br d, 2H), 3.13 (d, J=16.9, 1H), 3.36 (d, J=16.8), 3.62 (s, 3H), 3.69 (dt, J=11.7, 2.2, 1H), 4.03 (br s, 1H), 4.23–4.32 (m, 1H), 4.44 (d, J=13.3, 1H), 4.68, (d, J=2.6, 1H), 4.81 (d, J=13.5, 1H), 7.30–7.38 (m, 3H), 7.4–7.5 (m, 3H), 7.70 (s, 1H).

Analysis Calcd for $C_{22}H_{21}F_6NO_4$: C, 55.35; H, 4.43; N, 2.93; F, 23.88 Found: C, 55.09; H, 4.43; N, 2.83; F, 24.05

EXAMPLE 47

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-4-(carboxymethyl)-3-(S)-phenylmorpholine

A solution of 0.016 g (0.034 mmole) of 2-(S)-(3,5-Bis (trifluoromethyl)benzyloxy)-4-(methoxy-carbonylmethyl)-

3-(S)-phenylmorpholine (from Example 46) in 2 mL of THF and 0.5 mL of water was treated with 0.027 mL (0.067 mmole) of 2.5N aqueous sodium hydroxide and the mixture was stirred at room temperature for 5 hr. The mixture was treated with 2 drops of 2N aqueous HCl and 3 mL of water and the solution was extracted with 15 mL of 1:1 hexanes:ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography on 13 g of silica fluting with 250 mL of 100:3:0.1 methylene chloride:methanol:acetic acid then 100 mL of 50:2:0.1 methylene chloride:methanol:acetic acid to give 0.014 g (90%) of an oil.

Mass Spectrum (FAB): m/Z 464 (M+H, 90%), 420 (M—CO_2, 10%), 227 ($ArCH_2$, 35%), 220 (M—OCH_2Ar, 100%), 161 (20%).

^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 2.9 (app d, 2H), 3.03 (d, 1H), 3.33 (d, 1H), 3.72 (d, 1H), 3.90 (d, 1H), 4.25 (t, 1H), 4.44 (d, 1H), 4.71 (d, 1H), 4.79 (d, 1H), 7.3–7.4 (m, 5H), 7.44 (s, 2H), 7.71 (s, 1H).

EXAMPLE 48

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)4-((2-aminoethyl)aminocarbonylmethyl)-3-(S)-phenylmorpholine hydrochloride

A solution of 54 mg (0.11 mmole) of 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(carboxymethyl)-3-(S)-phenylmorpholine (from Example 46) and 0.15 mL of ethylenediamine (2.3 mmole) in 1 mL of methanol was stirred at 55° C. for 48 hr. The mixture was concentrated and the residue purified by flash chromatography on 16 g of silica eluting with 500 mL of 50:4:0.1 methylene chloride:methanol:aqueous ammonia to provide 57 mg (100%) of an oil. The oil was dissolved in ether and was treated with ether saturated with gaseous HCl. After concentration in vacuo, 58 mg (95%) of a rigid oil was obtained.

Mass Spectrum (FAB; free base): m/Z 506 (M+H, 100%), 418 (15%), 262(35%), 227 (30%), 173 (40%)

^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 2.56 (d, J=15.5, 1H), 2.59 (td, J=12.0, 3.6, 1H), 2.82 (t, J=6.5, 2H), 2.96 (d, J=11.8, 1H), 3.21 (d, J=15.8, 1H), 3.25–3.40 (m, 2H), 3.65 (d, J=2.6, 1H), 3.67 (app dt, J=11.4, ~2, 1H), 4.18 (td, J=11.8, 2.6, 1H), 4.33 (d, J=13.5, 1H),4.69 (d, J=2.7, 1H), 4.79 (d, J=13.5, 1H), 7.25–7.40 (m, 5H), 7.46 (s, 2H), 7.59 (br t, 1H), 7.71 (s, 1H).

EXAMPLE 49

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-4-((3-amino-propyl)amino carbonylmethyl)-3-(S)-phenylmorpholine hydrochloride

A solution of 59 mg (0.12 mmole) of 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(carboxymethyl)-3-(S)-phenylmorpholine (from Example 46) and 0.21 mL of 1,3-propylenediamine (2.5 mmole) in 1 mL of methanol was stirred at 55° C. for 72 hr. The mixture was concentrated and the residue purified by flash chromatography on 16 g of silica eluting with 500 mL of 10:1:0.05 methylene chloride:methanol:aqueous ammonia to provide 56 mg (88%) of an oil. The oil was dissolved in methylene chloride and was treated with methylene chloride saturated with gaseous HCl. After concentration in vacuo, a white paste was obtained.

Mass Spectrum (FAB; free base): m/Z 520 (M+H, 100%), 418 (10%), 276(30%), 227 (20%), 174 (30%)

^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 1.64 (pentet, J=6.6, 2H), 2.53 (d, J=15.5, 1H), 2.58 (td, J=12.0, 3.6, 1H), 2.73 (t, J=6.5, 2H), 2.92 (d, J=11.8, 1H), 3.19 (d, J=15.8, 1H), 3.25–3.40 (m, 2H), 3.62 (d, J=2.6, 1H), 3.65 (app dt, J=11.4, ~2, 1H), 4.16 (td, J=11.8, 2.6, 1H), 4.41 (d, J=13.5, 1H),4.68 (d, J=2.7, 1H), 4.79 (d, J=13.5, 1H), 7.25–7.40 (m, 5H), 7.45 (s, 2H), 7.57 (br t, 1H), 7.70 (s, 1H).

EXAMPLE 50

4-benzyl-5-(S),6-(R)-dimethyl-3-(S)-phenylmorpholinone and 4-benzyl-5-(R),6-(S)-dimethyl-3-(S)-phenylmorpholine

To a suspension of 1.7 g (7.0 mmole) of N-benzyl-(S)-phenylglycine (Example 13) in 15 ml of methylene chloride at 0° C. was added 6.9 ml (13.9 mmole) of trimethylaluminum (2.0M in toluene). After one hour at 0° C., 0.625 ml (7.0 mmole) of (±)-trans-2,3-epoxy butane (dissolved in 2.0 ml of methylene chloride) was added dropwise and then allowed to stir at 22° C. for 16 hours. The reaction was then transferred to another flask containing 30 ml of 1:1 hexane:methylene chloride and 30 ml of 1M potassium sodium tartrate and stirred at 22° C. for 2 hours. The layers were separated, and the aqueous layer was extracted with methylene chloride (3×100 ml). The combined organic layers were washed with 25 ml of a saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo.

The crude alcohol was dissolved in 25 ml of toluene, treated with 93 mg (0.49 mmole) of p-toluenesulfonic acid and heated at 50° C. for 20 hours. The reaction was then cooled and concentrated in vacuo. The residue was partitioned between 15 ml of diethyl ether and 10 ml of saturated sodium bicarbonate. The layers were separated, and the organic layer was washed with water (3×10 ml). The combined organic layers were washed with 25 ml of a saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated in VacuO. Flash chromatography on 145 g of silica gel using 1:4 v/v ethyl acetate/hexane as the eluant afforded 567 mg of the high R_f lactone (Isomer A) and 388 mg of the low R_f lactone (Isomer B).

^{1}H-NMR (400 MHz, $CDCl_3$) δ Isomer A: 1.04 (d, 3H, J=8.0 Hz), 1.24 (d, 3H, J=8.0 Hz), 2.92 (br qd, 1H), 3.41 (d, 1H, J=16.0 Hz), 3.62 (d, 1H, J=16.0 Hz), 4.38 (s, 1H), 4.96 (br qd, 1H), 7.20–7.42 (m, 8H), 7.58–7.64 (m, 2H); Isomer B: 1.04 (d, 3H, J=10.0 Hz), 1.39 (d, 3H, J=10.0 Hz), 3.06 (br qd, 1H), 3.53 (d, 1H, J=16.0 Hz), 3.81 (d, 1H, J=16.0 Hz), 4.33 (s, 1H), 4.67 (br qd, 1H), 7.18–7.50 (m, 10H). Mass Spectrum (FAB): m/z Isomer A: 296 (M+H, 100%), 294 (50%); Isomer B: 296 (M+H, 100%), 294 (50%).

EXAMPLE 51

2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-[5-(S),6-(R) or 5-(R),6-(S)-dimethyl]-3-(S)-phenylmorpholinone

Step A: 4-Benzyl-2-(R)-(3,5-bis(trifluoromethyl)-benzyloxy)-[5-(S),6-(R) or 5-(R),6-(S)-dimethyl]-3-(S)-phenylmorpholinone

According to the procedure in Example 15, Step B, 251 mg (0.85 mmole) of Isomer A from Example 50 (4-benzyl-[5-(S),6-(R) or 5-(R)-6-(S)-dimethyl]-3-(S)-phenylmorpholinone) provided 238 mg (53%) of the product as an oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.03 (d, 3H, J=6.7 Hz), 1.13 (d, 3H, J=6.6 Hz), 2.61 (qd, 1H, J=2.2 & 6.6 Hz), 3.26 (d, 1H, J=13.9 Hz), 3.55 (d, 1H, J=13.9 Hz), 3.63 (d, 1H,

J=7.6 Hz), 4.01 (qd, 1H, J=2.3 & 6.6 Hz), 4.44 (d, 1H, J=13.1 Hz), 4.53 (d, 1H, J=7.7 Hz), 4.71 (s, 1H), 4.85 (d, 1H, J=13.2 Hz), 7.20–7.35 (m, 9H), 7.46–7.48 (m, 2H), 7.67 (s, 1H), 7.81 (s, 1H).

Mass Spectrum (FAB): m/z 523 (M+H, 100%), 296 (95%), 280 (40%), 227 (50%).

Step B: 2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-[5-(S),6-(R) or 5-(R),6-(S)-dimethyl]-3-(S)-phenylmorpholinone

According to the procedure in Example 15, Step C, 260 mg of starting material from Step A [derived from Isomer A in Example 50 (4-Benzyl-2-(R)-(3,5-bis(trifluoromethyl) benzyloxy)-[5-(S),6-(R) or 5-(R),6-(S)-dimethyl]-3-(S)-phenylmorpholinone)] provided 122 mg (57%) of the product as an oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.19 (d, 3H, J=6.5 Hz), 1.27 (d, 3H, J=6.7 Hz), 2.97 (qd, 1H, J=2.9 & 6.9 Hz), 3.96 (d, 1H, J=7.7 Hz), 4.08–4.11 (m, 2H), 4.39 (d, 1H, J=7.7 Hz), 4.50 (d, 1H, J=13.3 Hz), 4.88 (d, 1H, J=13.2 Hz), 7.27–7.33 (m, 3H), 7.40–7.42 (m, 4H), 7.67 (s, 1H). Mass Spectrum (FAB): m/z 434 (M+H, 45%), 227 (35%), 206 (40%), 190 (100%).

EXAMPLE 52

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-[5-(R),6-(S) or 5-(S),6-(R)-dimethyl]-3-(S)-phenylmorpholinone

Step A: 4-Benzyl-2-(S)-(3,5-bis(trifluoromethyl)-benzyloxy)-[5-(R),6-(S) or 5(S),6-(R)-dimethyl]-3-(S)-phenylmorpholinone

According to the procedure in Example 15, Step B, 449 mg (1.52 mmole) of Isomer B from Example 50 (4-benzyl-[5-(R),6-(S) or 5-(S)-6-(R)-dimethyl]-3-(S)-phenylmorpholinone) provided 400 mg (51%) of the product as an oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.90 (d, 3H, J=6.8 Hz), 1.37 (d, 3H, J=6.6 Hz), 2.86–2.89 (br qd, 1H), 3.47 (d, 1H, J=15.0 Hz), 3.82–3.85 (m, 2H), 3.99–4.02 (br qd, 1H), 4.45 (d, 1H, J=13.6 Hz), 4.81 (d, 1H, J=2.0 Hz), 4.87 (d, 1H, J=13.5 Hz), 7.17–7.83 (m, 13H).

Step B: 2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-[5-(S),6-(R) or 5-(R),6-(S)-dimethyl]-3-(S)-phenylmorpholinone

According to the procedure in Example 15, Step C, 400 mg of starting material from Step A [derived from Isomer B in Example 50 (4-Benzyl-2-(S)-(3,5-bis(trifluoromethyl) benzyloxy)-[5-(R),6-(S) or 5-(S),6-(R)-dimethyl]-3-(S)-phenylmorpholinone)]provided 230 mg (69%) of the product as an oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.08 (d, 3H, J=6.7 Hz), 1.38 (d, 3H, J=7.0 Hz), 3.41–3.45 (br qd, 1H), 3.85–3.89 (br qd, 1H), 4.16 (d, 1H, J=2.9 Hz), 4.49 (d, 1H, J=13.6 Hz), 4.71 (d, 1H, J=2.9 Hz), 4.82 (d, 1H, J=13.6 Hz), 7.25–7.36 (m, 7H), 7.66 (s, 1H).

Mass Spectrum (FAB): m/z 434 (M+H, 35%), 227 (40%), 206 (40%), 190 (100%).

EXAMPLE 53

2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-4-(3-(1,2,4-triazolo)methyl)-[5-(S),6-(R) or 5-(R),6-(S)-dimethyl]-3-(S)-phenylmorpholinione

A mixture of 62 mg (0.14 mmole) of 2-(R)-(3,5-Bis (trifluoromethyl)benzyloxy)-[5-(S),6-(R) or 5-(R),6-(S)-dimethyl]-3-(S)-phenylmorpholinone (from Example 51, Step B), 62 mg (0.45 mmole) of anhydrous potassium carbonate and 26 mg (0.19 mmole) of N-formyl-2-chloroacetamidrazone (from Example 17, Step A) in 2.0 ml of N,N-dimethylformamide was heated to 60° C. for 2 hours and then 118° C. for 1.5 hours. The mixture was then allowed to cool to room temperature and then quenched with 5 mls of water and diluted with 15 mls of ethyl acetate. The layers were separated and the organic layer was washed with ethyl acetate (2×10 mls). The combined organic layers were washed with 10 mls of brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography on 42 g of silica gel using 95:5 v/v methylene chloride/methanol as the eluant afforded 42 mg (57%) of a clear oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.13 (d, 3H, J=6.5 Hz), 1.19 (d, 3H, J=6.5 Hz), 2.65 (qd, 1H, J=1.9 & 6.5 Hz), 3.58 (d, 1H, J=15.5 Hz), 3.65 (d, 1H, J=7.7 Hz), 3.75 (d, 1H, J=15.4 Hz), 4.06 (qd, 1H, J=2.2 & 6.6 Hz), 4.45 (d, 1H, J=13.2 Hz), 4.54 (d, 1H, J=7.7 Hz), 4.84 (d, 1H, J=13.2 Hz), 7.28–7.37 (m, 7H), 7.67 (s, 1H), 7.89 (s, 1H). Mass Spectrum (FAB): m/z 516 (M+H, 52%), 287 (28%), 271 (100%), 227 (40%), 202 (38%).

EXAMPLE 54

2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-4-(3-(5-oxo-1,2,4-triazolo)methyl)-[5-(S),6-(R) or 5-(R),6-(S)-dimethyl]-3-(S)-phenylmorpholinone

A solution of 96 mg (0.22 mmole) of 2-(R)-(3,5-Bis (trifluoromethyl)benzyloxy)-[5-(S),6-(R) or 5-(R),6-(S)-dimethyl]-3-(S)-phenylmorpholinone (from Example 51, Step B), 92 mg (0.66 mmole) of potassium carbonate and 48 mg (0.29 mmole) of N-methylcarboxy-2-chloroacetamidrazone (from Example 18, Step A) in 4 mL of DMF was heated at 60° C. for 1.5 hr and at 120° C. for 3.5 hr. The mixture was cooled to room temperature and was partitioned between 15 mL of water and 25 mL of ethyl acetate. The aqueous layer was extracted with 3×10 mL of ethyl acetate, the combined organic layers were washed with 10 mL of brine, dried over sodium sulfate, filtered and concentrated in vacuo. The residue was partly purified by flash chromatography on 42 g of silica gel using 2 L of 98:2 v/v methylene chloride/methanol as the eluant and the rich cuts were purified under the same conditions to give 38 mg (33%) of a clear oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.09 (d, 3H, J=6.5 Hz), 1.20 (d, 3H, J=6.6 Hz), 2.64 (qd, 1H, J=2.4 & 6.6 Hz), 3.33 (s, 1H), 3.56 (d, 1H, J=7.6 Hz), 4.11 (qd, 1H, J=2.4 & 6.6 Hz), 4.41 (d, 1H, J=13.2 Hz), 4.57 (d, 1H, J=7.7 Hz), 4.82 (d, 1H, J=13.2 Hz), 7.25–7.30 (m, 5H), 7.40 (d, 2H, J=5.7 Hz), 7.65 (s, 1H), 9.46 (s, 1H), 10.51 (s, 1H).

Mass Spectrum (FAB): m/z 531 (M+H, 98%), 287 (100%), 227 (80%), 189 (65%).

EXAMPLE 55

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-4-(3-(1,2,4-triazolo)methyl)-[5-(R),6-(S) or 5-(S),6-(R)-dimethyl]-3-(S)-phenylmorpholinone

According to the procedure in Example 53, 75 mg (0.17 mmole) of 2-(S)-(3,5-Bis(trifluoromethyl)-benzyloxy)-[5-(R),6-(S) or 5-(S),6-(R)-dimethyl]-3-(S)-phenylmorpholinone (from Example 52, Step B) provided, after flash chromatography on 73 g of silica gel using 98:2 v/v methylene chloride/methanol as the eluant, 46 mg (52%) of a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.04 (d, 3H, J=6.6 Hz), 1.46 (d, 3H, J=6.7 Hz), 3.05–3.08 (m, 1H), 3.74–3.81 (m, 2H), 3.91–3.95 (m, 2H), 4.41 (d, 1H, J=13.2 Hz), 4.69 (d, 1H, J=3.2 Hz), 4.82 (d, 1H, J=13.5 Hz), 7.31–7.35 (m, 5H), 7.43–7.45 (m, 2H), 7.68 (s, 1H), 7.91 (s, 1H).

Mass Spectrum (EI): m/z 432 (36%), 287 (60%), 270 (65%), 227 (30%), 187 (48%), 83 (100%).

EXAMPLE 56

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-4-(3-(5-oxo-1,2,4-triazolo)methyl)-[5-(R),6-(S) or 5-(S),6-(R)-dimethyl]-3-(S)-phenylmorpholinone

According to the procedure in Example 54, 86 mg (0.2 mmole) of 2-(S)-(3,5-Bis(trifluoromethyl)-benzyloxy)-[5-(R),6-(S) or 5-(S),6-(R)-dimethyl]-3-(S)-phenylmorpholinone (from Example 47, Step B) provided, after flash chromatography on 73 g of silica gel using 95:5 v/v methylene chloride/methanol as the eluant, 32 mg (30%) of a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.03 (d, 3H, J=6.7 Hz), 1.40 (d, 3H, J=6.8 Hz), 3.00 (qd, 1H, J=3.8 & 6.8 Hz), 3.44 (d, 1H, J=16.1 Hz), 3.63 (d, 1H, J=16.0 Hz), 3.82 (d, 1H, J=3.3 Hz), 3.95 (qd, 1H, J=3.7 & 6.7 Hz), 4.43 (d, 1H, J=13.5 Hz), 4.73 (d, 1H, J=3.3 Hz), 4.84 (d, 1H, J=13.6 Hz), 7.28–7.47 (m, 7H), 7.68 (s, 1H), 9.52 (d, 2H).

Mass Spectrum (FAB): m/z 531 (M+H, 100%), 287 (55%), 227 (25%), 147 (50%).

EXAMPLE 57

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-4-(2-(1-(4-benzyl)piperidino)ethyl)-3-(S)-phenylmorpholine

To a solution of 2-(S)-(3,5-bis(trifluoro-methyl) benzyloxy)-3-(S)-phenylmorpholine (50 mg, 0.12 mmol) and 4-benzyl-1-(2-chloroethyl)piperidine hydrochloride (50 mg, 0.18 mmol) in acetonitrile (0.5 mL) was added diisopropylethylamine (0.065 mL, 0.36 mmol) at room temperature. After 60 hours, TLC (5% MeOH/2% Et_3N/93% EtOAc) indicated that the reaction was only partially complete. The reaction was diluted with methylene chloride and washed with water, then brine, dried over sodium sulfate and evaporated. Prep TLC (5% MeOH/2% Et_3N/93% EtOAc) afforded 36 mg (50%) of the title compound as an oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.1–1.4 (m, 2H), 1.4–1.65 (2 m, 4H), 1.65–2.05 (m, 3H), 2.05–2.3 (m, 1H), 2.35–2.5 (m and d, J=7 Hz, 3H), 2.55 (br t, J=11 Hz, 1H), 2.65–2.8 (m, 2H), 3.09 (d, J=11 Hz, 1H), 3.50 (d, J=2.5 Hz, 1H), 3.66 (dd, J=2 and 11 Hz, 1H), 4.15 (dt, J=2 and 12 Hz, 1H), 4.38 and 4.75 (AB q, J=13 Hz, 2H), 4.61 (d, J=2.5 Hz, 1H), 7.06 (d, J=7 Hz, 2H), 7.15 (t, J=7 Hz, 1H), 7.2–7.35 (m, 5H), 7.36 (m, 4H), 7.75 (s, 1H).

EXAMPLE 58

(S)-(4-Fluorophenyl)glycine

Via Chiral Synthesis:

Step A: 3-(4-Fluorophenyl)acetyl-4-(S)-benzyl-2-oxazolidinone

An oven-dried, 1 L 3-necked flask, equipped with a septum, nitrogen inlet, thermometer, and a magnetic stirring bar, was flushed with nitrogen and charged with a solution of 5.09 g (33.0 mmol) of 4-fluorophenylacetic acid in 100 mL of anhydrous ether. The solution was cooled to −10° C. and treated with 5.60 mL (40.0 mmol) of triethylamine followed by 4.30 mL (35.0 mmol) of trimethylacetyl chloride. A white precipitate formed immediately. The resulting mixture was stirred at −10° C. for 40 minutes, then cooled to −78° C.

An oven-dried, 250 mL round bottom flask, equipped with a septum and a magnetic stirring bar, was flushed with nitrogen and charged with a solution of 5.31 g (30.0 mmol) of 4-(S)-benzyl-2-oxazolidinone in 40 mL of dry THF. The solution was stirred in a dry ice/acetone bath for 10 minutes, then 18.8 mL of 1.6M n-butyllithium solution in hexanes was slowly added. After 10 minutes, the lithiated oxazolidinone solution was added, via cannula, to the mixture in the 3-necked flask. The cooling bath was removed from the resulting mixture and the temperature was allowed to rise to 0° C. The reaction was quenched with 100 mL of saturated aqueous ammonium chloride solution, transferred to a 1 L flask, and the ether and THF were removed in vacuo. The concentrated mixture was partitioned between 300 mL of methylene chloride and 50 mL of water and the layers were separated. The organic layer was washed with 200 mL of 2N aqueous hydrochloric acid solution, 300 mL of saturated aqueous sodium bicarbonate solution, dried over magnesium sulfate and concentrated in vacuo. Flash chromatography on 400 g of silica gel using 3:2 v/v hexanes/ether as the eluant afforded 8.95 g of an oil that slowly solidified on standing. Recrystallization from 10:1 hexanes/ether afforded 7.89 g (83%) of the title compound as a white solid, mp 64°–66° C. Mass Spectrum (FAB): m/Z 314 (M+H, 100%), 177 (M—$ArCH_2CO$+H, 85%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.76 (dd, 1H, J=13.2, 9.2), 3.26 (dd, J=13.2, 3.2), 4.16–4.34 (m, 4H), 4.65–4.70 (m, 1H), 7.02–7.33 (m, 9H). Analysis: Calcd for $C_{18}H_{16}FNO_3$: C, 69.00; H, 5.15; N, 4.47; F, 6.06 Found: C, 68.86; H, 5.14; N, 4.48; F, 6.08

Step B: 3-((S)-Azido-(4-fluorophenyl))acetyl-4-(S)-benzyl-2-oxazolidinone

An oven-dried, 1 L 3-necked flask, equipped with a septum, nitrogen inlet, thermometer, and a magnetic stirring bar, was flushed with nitrogen and charged with a solution of 58.0 mL of 1M potassium bis(trimethylsilyl)amide solution in toluene and 85 mL of THF and was cooled to −78° C. An oven-dried, 250 mL round-bottomed flask, equipped with a septum and a magnetic stirring bar, was flushed with nitrogen and charged with a solution of 7.20 g (23.0 mmol) of 3-(4-fluorophenyl)acetyl-4-(S)-benzyl-2-oxazolidinone (from Example 58, Step A) in 40 mL of THF. The acyl oxazolidinone solution was stirred in a dry ice/acetone bath for 10 minutes, then transferred, via cannula, to the potassium bis(trimethylsilyl)amide solution at such a rate that the internal temperature of the mixture was maintained below −70° C. The acyl oxazolidinone flask was rinsed with 15 mL of THF and the rinse was added, via cannula, to the reaction mixture and the resulting mixture was stirred at −78° C. for 30 minutes. An oven-dried, 250 mL round-bottomed flask, equipped with a septum and a magnetic stirring bar, was flushed with nitrogen and charged with a solution of 10.89 g (35.0 mmol) of 2,4,6-triisopropylphenylsulfonyl azide in 40 mL of THF. The azide solution was stirred in a dry ice/acetone bath for 10 minutes, then transferred, via cannula, to the reaction mixture at such a rate that the internal temperature of the mixture was maintained below −70° C. After 2 minutes, the reaction was quenched with 6.0 mL of glacial acetic acid, the cooling bath was removed and the mixture was stirred at room temperature for 18 hours. The quenched reaction mixture was partitioned between 300 mL of ethyl acetate and 300 mL of 50% saturated aqueous

sodium bicarbonate solution. The organic layer was separated, dried over magnesium sulfate, and concentrated in vacuo. Flash chromatography on 500 g of silica gel using 2:1 v/v, then 1:1 v/v hexanes/methylene chloride as the eluant afforded 5.45 g (67%) of the title compound as an oil.

IR Spectrum (neat, cm^{-1}): 2104, 1781, 1702.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.86 (dd, 1H, J=13.2, 9.6), 3.40 (dd, 1H, J=13.2, 3.2), 4.09–4.19 (m, 2H), 4.62–4.68 (m, 1H), 6.14 (s, 1H), 7.07–7.47 (m, 9H).

Analysis: Calcd for $C_{18}H_{15}FN_4O_3$: C, 61.01; H, 4.27; N, 15.81; F, 5.36 Found: C, 60.99; H, 4.19; N, 15.80; F, 5.34

Step C: (S)-Azido-(4-fluorophenyl)acetic acid

A solution of 5.40 g (15.2 mmol) of 3-((S)-azido-(4-fluorophenyl))acetyl-4-(S)-benzyl-2-oxazolidinone (from Example 58, Step B) in 200 mL of 3:1 v/v THF/water was stirred in an ice bath for 10 minutes. 1.28 g (30.4 mmol) of lithium hydroxide monohydrate was added in one portion and the resulting mixture was stirred cold for 30 minutes. The reaction mixture was partitioned between 100 mL of methylene chloride and 100 mL of 25% saturated aqueous sodium bicarbonate solution and the layers were separated. The aqueous layer was washed with 2×100 mL of methylene chloride and acidified to pH with 2N aqueous hydrochloric acid solution. The resulting mixture was extracted with 2×100 mL of ethyl acetate; the extracts were combined, washed with 50 mL of saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo to afford 2.30 g (77%) of the title compound as an oil that was used in the following step without further purification.

IR Spectrum (neat, cm–1): 2111, 1724. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.06 (s, 1H), 7.08–7.45 (m, 4H), 8.75 (br s, 1H).

Step D: (S)-4-Fluorophenyl)glycine

A mixture of 2.30 g (11.8 mmol) of (S)-azido-(4-fluorophenyl)acetic acid (from Example 58, Step C), 250 mg 10% palladium on carbon catalyst and 160 mL 3:1 v/v water/acetic acid was stirred under an atmosphere of hydrogen for 18 hours. The reaction mixture was filtered through Celite and the flask and filter cake were rinsed well with ~1 L of 3:1 v/v water/acetic acid. The filtrate was concentrated in .vacuo to about 50 mL of volume. 300 mL of toluene was added and the mixture concentrated to afford a solid. The solid was suspended in 1:1 v/v methanol/ether, filtered and dried to afford 1.99 g (100%) of the title compound.

^{1}H-NMR (400 MHz, D_2O+NaOD): δ 3.97 (s, 1H), 6.77 (app t, 2H, J=8.8), 7.01 (app t, 2H, J=5.6).

Via Resolution:

Step A': 4-Fluorophenylacetyl chloride

A solution of 150 g (0.974 mol) of 4-fluorophenylacetic acid an 1 mL of N,N-dimethylformamide in 500 mL of toluene at 40° C. was treated with 20 mL of thionyl chloride and heated to 40° C. An additional 61.2 mL of thionyl chloride was added dropwise over 1.5 hours. After the addition, the solution was heated at 50° C. for 1 hour, the solvent was removed in vacuo and the residual oil was distilled at reduced pressure (1.5 mmHg) to afford 150.4 g (89.5%) of the title compound, bp=68°–70° C.

Step B': Methyl 2-bromo-2-(4-fluoro)phenylacetate

A mixture of 150.4 g (0.872 mol) of 4-fluorophenylacetyl chloride (from Example 58, Step A') and 174.5 g (1.09 mol) of bromine was irradiated at 40°–50° C. with a quartz lamp for 5 hours. The reaction mixture was added dropwise to 400 mL of methanol and the solution was stirred for 16 hours. The solvent was removed in vacuo and the residual oil was distilled at reduced pressure (1.5 mmHg) to afford 198.5 g (92%) of the title compound, bp=106°–110° C.

Step C': Methyl (±)-(4-fluorophenyl)glycine

A solution of 24.7 g (0.1 mol) of methyl 2-bromo-2-(4-fluoro) phenylacetate (from Example 58, Step B') and 2.28 g (0.01 mol) of benzyl triethylammonium chloride in 25 mL of methanol was treated with 6.8 g (0.105 mol) of sodium azide and the resulting mixture was stirred 20 hours at room temperature. The reaction mixture was filtered; the filtrate was diluted with 50 mL of methanol and hydrogenated in the presence of 0.5 g of 10% Pd/C at 50 psi for 1 hour. The solution was filtered and the solvent removed in vacuo. The residue was partitioned between 10% aqueous sodium carbonate solution and ethyl acetate. The organic phase was washed with water, saturated aqueous sodium chloride solution, dried over magnesium sulfate and concentrated in vacuo to afford 9.8 g of the title compound as an oil.

Step D': Methyl (S)-(4-fluorophenyl)glycinate

A solution of 58.4 g of methyl (±)-4-fluorophenylglycinate (from Example 58, Step C') in 110 mL of 7:1 v/v ethanol/water was mixed with a solution of 28.6 g (0.0799 mol) of O,O'-(±)-dibenzoyltartaric acid ((+)-DBT) (28.6 g, 0.0799 mol) in 110 mL of 7:1 v/v ethanol:water and the resulting solution was allowed to age at room temperature. Ethyl acetate (220 ml) was added after crystallization was complete and the resulting mixture was cooled to –20° C. and filtered to afford 32.4 g of methyl (S)-(4-fluorophenyl) glycinate, (+)-DBT salt (ee=93.2%). The mother liquors were concentrated in vacuo and the free base was liberated by partitioning between ethyl acetate and aqueous sodium carbonate solution. A solution of free base, so obtained, in 110 mL of 7:1 v/v ethanol/water was mixed with a solution of 28.6 g (0.0799 mol) of O,O'-(–)-dibenzoyltartaric acid ((–)-DBT) (28.6 g, 0.0799mol) in 110 mL of 7:1 v/v ethanol:water and the resulting solution was allowed to age at room temperature. Ethyl acetate (220 ml) was added after crystallization was complete and the resulting mixture was cooled to –20° C. and filtered to afford 47.0 g of methyl (R)-(4-fluorophenyl) glycinate, (–)-DBT salt (ee=75.8%). Recycling of the mother liquors and addition of (+)-DBT gave a second crop of 7.4 g of (S)-(4-fluorophenyl) glycinate, (+)-DBT salt (ee=96.4%). The two crops of the (S)-amino ester (39.8 g) were combined in 200 mL of 7:1 v/v ethanol/water, heated for 30 minutes and cooled to room temperature. Addition of ethyl acetate, cooling, and filtration afforded 31.7 g of (S)-(4-fluorophenyl) glycinate, (+)-DBT salt (ee>98%). Enatiomeric excesses was determined by chiral HPLC (Crownpak CR(+) 5% MeOH in aq$HClO_4$ pH2 1.5 ml/min 40° C. 200 mm).

A mixture of 17.5 g of (S)-(4-fluorophenyl) glycinate, (+)-DBT salt and 32 mL of 5.5N HCl (32 ml) was heated at reflux for 1.5 hours. The reaction mixture was concentrated in vacuo and the residue was dissolved in 40 mL of water. The aqueous solution was washed 3×30 mL of ethyl acetate and the layers were separated. The pH of the aqueous layer was adjusted to 7 using ammonium hydroxide and the precipitated solid was filtered to afford 7.4 g of the title compound (ee=98.8%).

EXAMPLE 59

3-(S)-(4-Fluorophenyl)-4-benzyl-2-morpholinone

Step A: N-Benzyl (S)-4-fluorophenyl)glycine

A solution of 1.87 g (11.05 mmol) of (S)-(4-fluorophenyl) glycine (from Example 58) and 1.12 mL (11.1 mmol) of

benzaldehyde in 11.1 mL of 1N aqueous sodium hydroxide solution and 11 mL of methanol at 0° C. was treated with 165 mg (4.4 mmol) of sodium borohydride. The cooling bath was removed and the resulting mixture was stirred at room temperature for 30 minutes. Second portions of benzaldehyde (1.12 mL (11.1 mmol)) and sodium borohydride 165 mg (4.4 mmol) were added to the reaction mixture and stirring was continued for 1.5 hours. The reaction mixture was partitioned between 100 mL of ether and 50 mL of water and the layers were separated. The aqueous layer was separated and filtered to remove a small amount of insoluble material. The filtrate was acidified to pH 5 with 2N aqueous hydrochloric acid solution and the solid that had precipitated was filtered, rinsed well with water, then ether, and dried to afford 1.95 g of the title compound. ^{1}H-NMR (400 MHz, D_2O+NaOD): δ 3.33 (AB q, 2H, J=8.4), 3.85 (s, 1H), 6.79–7.16 (m, 4H).

Step B: 3-(S)-(4-Fluorophenyl)-4-benzyl-2-morpholinone

A mixture of 1.95 g (7.5 mmol) of N-benzyl (S)-(4-fluorophenyl)glycine, 3.90 mL (22.5 mmol) of N,N-diisopropylethylamine, 6.50 mL (75.0 mmol) of 1,2-dibromoethane and 40 mL of N,N-dimethylformamide was stirred at 100° C. for 20 hours (dissolution of all solids occurred on warming). The reaction mixture was cooled and concentrated in vacuo. The residue was partitioned between 250 mL of ether and 100 mL of 0.5N potassium hydrogen sulfate solution and the layers were separated. The organic layer was washed with 100 mL of saturated aqueous sodium bicarbonate solution, 3×150 mL of water, dried over magnesium sulfate, and concentrated in vacuo. Flash chromatography on 125 g of silica gel using 3:1 v/v hexanes/ether as the eluant afforded 1.58 g (74%) of the title compound as an oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.65 (dt, 1H, J=3.2, 12.8), 3.00 (dt, 1H, J=12.8, 2.8), 3.16 (d, 1H, J=13.6), 3.76 (d, 1H, J=13.6), 4.24 (s, 1H), 4.37 (dt, 1H, J=13.2, 3.2), 4.54 (dt, 1H, J=2.8, 13.2), 7.07–7.56 (m, 9H).

EXAMPLE 60

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-(4-fluorophenyl)-4-benzylmorpholine

The title compound was prepared in 72% yield from 3-(S)-(4-fluorophenyl)-4-benzyl-2-morpholinone (from Example 59) using procedures analogous to those in Example 15, Steps A and B.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.37 (dt, 1H, J=3.6, 11.8), 2.83–2.90 (m, 2H), 3.55–3.63 (m, 2H), 3.85 (d, 1H, J=13.4), 4.14 (dt, 1H, J=2.0, 11.8), 4.44 (d, 1H, J=13.6), 4.66 (d, 1H, J=2.8), 4.79 (d, 1H, J=13.4), 7.00–7.70 (12H).

EXAMPLE 61

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-(4-fluorophenyl)morpholinone

The title compound was prepared in 70% yield from 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-(4-fluorophenyl)-4-benzylmorpholine (from Example 60) using a procedure analogous to that in Example 15, Step C. Mass Spectrum (FAB): m/Z 424 (M+H, 40%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.80 (br s, 1H), 3.11 (app dd, 1H, J=2.2, 12.4), 3.25 (dt, 1H, J=3.6, 12.4), 3.65 (app dd, 1H, J=3.6, 11.4), 4.05 (dt, 1H, J=2.2, 11.8), 4.11 (d, 1H, J=2.2), 4.53 (d, 1H, J=13.6), 4.71 (d, 1H, J=2.2), 4.83 (d, 1H, J=13.6), 7.04 (t, 2H, J=7.2), 7.33–7.37 (m, 2H), 7.42 (s, 2H), 7.72 (s, 1H).

EXAMPLE 62

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo) methylmorphololine

The title compound was prepared in 69% yield from 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-(4-fluorophenyl)morpholine (from Example 61) using a procedure analogous to that in Example 18. Mass Spectrum (FAB): m/Z 521 (M+H, 100%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.55 (dt, 1H, J=3.6, 12.0), 2.91 (d, 1H, J=11.6), 2.93 (d, 1H, J=14.4), 3.57 (d, 1H, J=2.8), 3.59 (d, 1H, J=14.4), 3.67–3.70 (m, 1H), 4.18 (dt, 1H, J=2.4, 11.6), 4.48 (d, 1H, J=13.6), 4.65 (d, 1H, J=2.8), 4.84 (d, 1H, J=13.6), 7.07 (t, 2H, J=8.4), 7.40 (s, 2H), 7.45–7.48 (m, 2H), 7.68 (s, 1H), 10.04 (br s, 1H), 10.69 (br s, 1H).

Analysis: Calcd for $C_{22}H_{19}F_7N_4O_3$: C, 50.78; H, 3.68; N, 10.77; F, 25.55 Found: C, 50.89; H, 3.76; N, 10.62; F, 25.56

EXAMPLE 63

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-4-((3-pyridyl)methyl carbonyl)-3-(R)-phenylmorpholine

A solution of 55 mg (0.315 mmol) of 4-pyridylacetic acid in 1 mL of CH_2Cl_2, containing 0.079 mL (0.715 mmol) of N-methylmorpholine, 53 mg (0.37 mmol) of HOBt and 73 mg (0.37 mmol) of EDC was stirred for 10 min. A solution of 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenylmorpholine (from Example 33) in 1 mL of CH_2Cl_2 was added. After stirring the mixture for 2 h, it was partitioned between water and CH_2Cl_2. The organic layer was washed with water, brine and dried by filtering through Na_2SO_4. The filtrate was concentrated and the residue was purified by flash chromatography using 70% EtOAc/hexane to furnish 152 mg (100% yield) of the product.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.0–3.85 (m, 5H), 3.95 & 4.4 (br s, 1H), 4.66 (d, J=13 Hz, 1H), 4.82 (d, J=13 Hz, 1H), 5.0 & 5.9 (br s, 1H), 5.23 (s, 1H), 7.1–7.65 (m, 7H), 7.8 (m, 3H), 8.43 (br s, 2H).

EXAMPLE 64

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-4-(methoxycarbonylpentyl)-3-(R)-phenylmorpholine

To a solution of 0.259 g (0.64 mmol) of 2-(S)-(3,5-bis (trifluoromethyl)benzyloxy)-3-(R)-phenylmorpholine (from example 33) in 2 mL of DMF were added 0.16 g (0.77 mmol) of methyl 6-bromohexanoate, 0.155 g (1.12 mmol) of K_2CO_3 and 2 crystals of nBu_4NI. The resulting solution was heated in a 60° C. bath for 36 h, at which time a tlc indicated incomplete reaction. The bath temperature was raised to 100° C. After 3 h the reaction mixture was cooled and diluted with EtOAc. The EtOAc solution was washed with water (2×), brine and dried over Na_2SO_4. The filtrate was concentrated and the residue was chromatographed using 30% EtOAc/hexane to isolate 220 mg (65%) of the product.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.0–1.4 (m, 4H), 1.47 (m, J=8 Hz, 2H), 1.95 (m, 1H), 2.2 (t, J=8 Hz, 2H), 2.35 (m, 2H), 2.9 (d, J=13 Hz, 1H), 3.07 (d, J=7 Hz, 1H), 3.62 (s, 3H), 3.81 (td, J=8 Hz and 2 Hz, 1H), 4.04 (dd, J=10 Hz and 2 Hz, 1H), 4.36 (d, J=7 Hz, 1H), 4.4 (d, J=13 Hz, 1H), 4.79 (d, J=13 Hz, 1H), 7.2–7.4 (m, 7H), 7.66 (s, 1H).

EXAMPLE 65

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-4-(carboxypentyl)-3-(R)-phenylmorpholine

A solution of 0.15 g (0.28 mmol) of 2-(S)-(3,5-Bis (trifluoromethyl)benzyloxy)-4-(methoxycarbonylpentyl)-3-

(R)-phenylmorpholine (from Example 64) in 3 mL of MeOH was saponified by treating with 0.5 mL of 5N NaOH for 40 min at 65° C. The solution was cooled, concentrated and the residue was diluted with water. The aqueous solution was adjusted to pH 6 by adding 2N HCl and it was extracted with EtOAc. The organic layer was washed with brine, dried and concentrated. The residue upon chromatography on a flash column with 50% EtOAc/hexane furnished 0.13 g (89%) of the product.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.0–1.5 (m, 4H), 1.5 (m, 2H), 2.2 (m, 2H), 2.35 (m, 2H), 2.9 (d, J=13 Hz, 1H), 3.08 (d, J=7 Hz, 1H), 3.82 (t, J=8 Hz, 1H), 4.09 (d, J=7 Hz, 1H), 4.38 (s, 1H), 4.4 (d, J=13 Hz, 1H), 4.79 (d, J=13 Hz, 1H), 7.2–7.4 (m, 7H), 7.66 (s, 1H).

EXAMPLE 66

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-4-(methylaminocarbonylpentyl)-6-oxo-hexyl)-3-(R)-phenylmorpholine

A solution of 116 mg (0.22 mmol) of 2-(S)-(3,5-Bis (trifluoromethyl)benzyloxy)-4-(carboxypentyl)3-(R)-phenylmorpholine (from Example 65) in 1 mL of CH_2Cl_2 was treated with 40 mg (0.29 mmol) of HOBt, 57 mg (0.29 mmol) of EDC and 0.037 mL of N-methylmorpholine. After 10 min 0.027 mL (0.3 mmol) of aqueous methylamine (40%) was added and the resulting mixture was stirred for 4 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined CH_2Cl_2 layer was washed with water, brine and dried over Na_2SO_4, and the filtrate was concentrated. Purification of the residue on a flash column with EtOAc furnished 0.10 g of the product.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.0–1.4 (m, 4H), 1.47 (m, 2H), 1.95 (m, 1H), 2.04 (t, J=8 Hz, 2H), 2.35 (m, 2H), 2.74 (d, J=5 Hz, 3H), 2.89(d, J=12 Hz, 1H) 3.08 (d, J=7 Hz, 1H), 3.81 (t, J=7 Hz, 1H), 4.02 (d, J=11 Hz, 1H), 4.36 (d, J=7 Hz, 1H), 4.39 (d, J=13 Hz, 1H), 4.79 (d, J=13 Hz, 1H), 5.03 (br s, 1H), 7.2–7.4 (m, 7H), 7.65 (s, 1H).

EXAMPLE 67

2-(R)-(3,5-Bis(trifluoromethyl)benzoyloxy)-3-(S)-phenyl-4-benzyl morpholine

A solution of 2.67 g (10.0 mmol) of 3-(S)-phenyl-4-benzyl-2-morpholinone (from Example 14) in 40 mL of dry THF was cooled to −78° C. The cold solution was treated with 12.5 mL of 1.0M L-Selectride®, solution in THF, maintaining the internal reaction temperature below −70° C. Alternatively, only a 6% excess of L-Selectride® may be required. The resulting solution was stirred cold for 45 minutes and the reaction was charged with 3.60 mL (20.0 mmol) of 3,5-bis(trifluoro-methyl)benzoyl chloride. The resulting yellow mixture was stirred cold for 30 minutes and the reaction was quenched with 50 mL of saturated aqueous sodium bicarbonate solution. Alternatively, acetic acid may be used for the quench. The quenched mixture was partitioned between 300 mL of ether and 50 mL of water and the layers were separated. The organic layer was dried over magnesium sulfate. The aqueous layer was extracted with 300 mL of ether; the extract was dried and combined with the original organic layer. The combined organics were concentrated in vacuo. Flash chromatography on 150 g of silica gel using 37:3 v/v hexanes/ether as the eluant afforded 4.06 g (80%) of the title compound as a solid.

^{1}H NMR ($CDCl_2$, 200 MHz, ppm): δ 2.50 (dt, J=3.4, 12.0, 1H), 2.97 (app d, J=12.0, 1H), 2.99 (d, J=13.6, 1H), 3.72–3.79 (m, 1H), 3.82 (d, J=2.6, 1H), 4.00 (d, J=13.6, 1H), 4.20 (dt, J=2.4, 11.6), 6.22 (d, J=2.6, 1H), 7.22–7.37 (m, 7H), 7.57 (app d, J=6.8, 2H), 8.07 (s, 1H), 8.47 (s, 2H).

Analysis Calcd for $C_{26}H_{21}F_6NO_3$: C, 61.29; H, 4.16; N, 2.75; F, 22.38. Found: C, 61.18; H, 4.14; N, 2.70; F, 22.13.

EXAMPLE 68

2-(R)-(1-(3,5-Bis(trifluoromethyl)phenyl) ethenyloxy)-3-(S)-phenyl-4-benzyl morpholine

Step A: Dimethyl titanocene

A solution of 2.49 g (10.0 mmol) of titanocene dichloride in 50 mL of ether in the dark at 0° C. was treated with 17.5 mL of 1.4M methyllithium solution in ether maintaining the internal temperature below 5° C. The resulting yellow/orange mixture was stirred at room temperature for 30 minutes and the reaction was quenched by slowly adding 25 g of ice. The quenched reaction mixture was diluted with 50 mL of ether and 25 mL of water and the layers were separated. The organic layer was dried over magnesium sulfate and concentrated in vacuo to afford 2.03 g (98%) of the title compound as a light-sensitive solid. Alternatively, dimethyl titanocene may be prepared from methyl magnesium chloride. The dimethyl titanocene could be stored as a solution in toluene at 0° C. for at least 2 weeks without apparent chemical degradation. ^{1}H NMR ($CDCl_2$, 200 MHz, ppm): δ −0.15 (s, 6H), 6.06 (s, 10H).

Step B: 2-(R)-(1-(3,5-Bis(trifluoromethyl)phenyl) ethenyloxy)-3-(S)-phenyl-4-benzyl morpholine

A solution of 2.50 g (4.9 mmol) of 2-(R)-(3,5-bis (trifluoro-methyl)benzoyloxy)-3-(S)-phenyl-4-benzyl morpholine from Example 67) and 2.50 g (12.0 mmol) of dimethyl titocene (from Example 68, Step A) in 35 mL of 1:1 v/v THF/toluene was stirred in an oil bath at 80° C. for 16 hours. The reaction mixture was cooled and concentrated in vacuo. Flash chromatography on 150 g of silica gel using 3:1 v/v hexanes/methylene chloride as the eluant afforded 1.71 g (69%) of the title compound as a solid. Alternatively, the product may be isolated by crystallization from methanol, following precipitation of titanium residues. Mass Spectrum (FAB): m/Z 508 (M+H, 25%).

^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 2.42 (dt, J=3.6, 12.0, 1H), 2.89 (app d, J=11.6), 2.92 (d, J=13.6, 1H), 3.61–3.66 (m, 1H), 3.73 (d, J=2.8), 1H), 4.00 (d, J=13.6, 1H), 4.09 (dt, J=2.4, 11.6, 1H), 4.75 (d, J=2.8, 1H), 4.79 (d, J=2.8, 1H), 5.36 (d, J=2.4, 1H), 7.23–7.41 (m, 7H), 7.63 (app d, J=7.2, 2H), 7.79 (s, 1H), 7.91 (s, 2H).

Analysis Calcd for $C_{27}H_{23}F_6NO_2$: C, 63.90; H, 4.57; N, 2.76; F, 22.46. Found: C, 63.71; H, 4.53; N, 2.68; F, 22.66.

EXAMPLE 69

2-(R)-(1-(S)-(3,5-Bis(trifluoromethyl)phenyl) ethoxy)-3-(S)-phenyl morpholine and 2-(S)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-phenyl morpholine

A mixture of 1.50 g (2.9 mmol) of 2-(R)-(1-(3,5-bis (trifluoromethyl)phenyl)ethenyloxy)-3-(S)-phenyl-4-benzyl morpholine (from Example 68) and 750 mg 10% palladium on carbon catalyst in 25 mL of 3:2 v/v isopropanol/ethyl acetate was stirred under an atmosphere of hydrogen for 48 hours. Alternatively, the hydrogenation may be conducted using 5% palladium on alumina. The catalyst was filtered onto a pad of Celite; the reaction flask and filter pad were

rinsed with 500 mL of ethyl acetate. The filtrate was concentrated in vacuo. Flash chromatography on 60 g of silica gel using 2:1 v/v hexanes/ether, then 2:1 v/v hexanes/ether afforded 106 mg of 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-phenyl morpholine and 899 mg of 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl) ethoxy)-3-(S)-phenyl morpholine, both as oils (84% total yield).

For 2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl) ethoxy)-3-(S)-phenyl morpholine:

Mass Spectrum (CI): m/Z 420 (M^+, 20%), 178 (100%).

^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 1.46 (d, J=6.8), 1.92 (br s, 1H), 3.13 (dd, J=3.0, 12.6, 1H), 3.24 (dt, J=3.6, 12.6, 1H), 3.62 (rid, J=3.6, 11.2), 4.04 (d, J=2.4, 1H), 4.14 (dt, J=3.0, 11.2, 1H), 4.48 (d, J=2.4, 1H), 4.90 (q, J=6.8, 1H), 7.21–7.32 (m, 7H), 7.64 (s, 1H).

Analysis Calcd for $C_{20}H_{19}F_6NO_2$: C, 57.28; H, 4.57; N, 3.34; F, 27.18. Found: C, 57.41; H, 4.61; N, 3.29; F, 27.23.

EXAMPLE 70

2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl) ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo) methylmorpholine

Step A: 2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl) phenyl)ethoxy)-3-(S)-phenyl-4-(2-(N-methylcarboxy-acetamidrazono)morpholine

A solution of 945 mg (2.3 mmol) of 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-phenyl morpholine (from Example 69), 447 mg (2.7 mmol) of N-methylcarboxy-2-chloroacetamidrazone (from Example 45, Step A), and 0.78 mL (4.5 mmol) of N,N-diisopropylethylamine in 17 mL of acetonitrile was stirred at room temperature for 20 hours. Alternatively, the alkylation may be conducted in dimethyl sulfoxide using potassium carbonate as a base. The reaction was concentrated in vacuo and the residue was partitioned between 50 mL of methylene chloride and 25 mL of water. The organic layer was separated, dried over magnesium sulfate and concentrated in vacuo. Flash chromatography on 50 g of silica gel using 50:1:0.1 methylene chloride/methanol/ammonium hydroxide as the eluant afforded 1.12 g (90%) of the title compound as a foam.

Step B: 2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl) phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methylmorpholine

A solution of 1.01 g (1.8 mmol) of 2-(R)-(1-(R)-(3,5-bis (trifluoromethyl)phenyl)ethoxy)-3-(S)-phenyl-4-(2-(N-methylcarboxyacetamidrazono)morpholine (from Example 70, Step A) in 15 mL of xylenes was heated at reflux for 2 hours. Diisopropylethylamine is optionally present. The reaction was cooled and concentrated in vacuo. Flash chromatography on 50 g of silica gel using 50:1:0.1 methylene chloride/methanol/ammonium hydroxide as the eluant afforded 781 mg (76%) of the title compound as a solid. The crude product may also be isolated directly upon cooling the reaction mixture. The purified product may be afforded by crystallization from hot methanol (charcoal decolorization) and water trituration.

Mass Spectrum (FAB) m/Z 517 (M+H, 18%), 178 (100%).

^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 1.47 (d, J=6.8), 2.01–2.05 (m, 2H), 2.55 (dt, J=3.6, 12.0, 1H), 2.91 (d, J=10.8, 1H), 2.95 (d, J=14.8, 1H), 3.49 (d, J=2.4, 1H), 3.65 (d, J=14.8, 1H), 3.69 (d, J=10.8, 1H), 4.29 (dt, J=2.4, 10.0), 4.38 (d, J=2.8, 1H), 4.88 (q, J=6.8, 1H), 7.14 (s, 2H), 7.33–7.40 (m, 5H), 7.62 (s, 1H), 9.91 (br s, 1H), 10.16 (br s, 1H).

Analysis Calcd for $C_{23}H_{22}F_6N_4O_3$: C, 53.49; H, 4.06; N, 10.85; F, 22.07. Found: C, 53.64; H, 4.33; N, 10.81; F, 22.27.

EXAMPLE 71

2-(R)-(1-(S)-(3,5-Bis(trifluoromethyl)phenyl) ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo) methylmorpholine

The title compound was prepared in 32% yield from 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-phenyl morpholine (from Example 69) using a procedure analogous to Example 70.

Mass Spectrum (FAB): m/Z 517 (M+H, 100%), 259 (50%).

^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 1.09 (d, J=6.4, 3H), 2.47–2.53 (m, 1H), 2.83 (app d, J=11.6, 1H), 2.95 (d, J=14.0, 1H), 3.51–3.65 (m, 3H), 4.01 (app t, J=11.6, 1H), 4.60 (q, J=6.4, 1H), 4.84 (d, J=2.4, 1H), 7.33–7.51 (m, 5H), 7.74 (s, 2H), 7.76 (s, 1H), 9.51 (br s, 1H), 10.00 (br s, 1H).

EXAMPLE 72

2-(R)-(3,5-Bis(trifluoromethyl)benzoyloxy)-3-(S)-(4-fluoro)phenyl-4-benzyl morpholine

The title compound was prepared in 83% yield from 3-(R)-(4-fluoro)phenyl-4-benzyl-2-morpholinone (from Example 59) using a procedure analogous to Example 67.

Mass Spectrum (FAB): m/Z 528 (M+H, 25%), 270 (100%).

^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 2.50 (dt, J=3.2, 12.0, 1H), 2.96 (app d, J=12.0, 1H), 2.98 (d, J=13.6, 1H), 3.74–3.78 (m, 1H), 3.81 (d, J=2.8, 1H), 3.94 (d, J=13.6, 1H), 4.19 (tit, J=2.0, 12.0), 6.20 (d, J=2.8, 1H), 6.99 (t, J=8.4, 2H), 7.27–7.38 (m, 5H), 7.52–7.56 (m, 2H), 8.09 (s, 1H), 8.46 (s, 2H).

EXAMPLE 73

2-(R)-(1-(3,5-Bis(trifluoromethyl)phenyl) ethenyloxy)-3-(S)-(4-fluoro)phenyl-4-benzyl morpholine

The title compound was prepared in 60% yield from 2-(R)-(3,5-bis(trifluoromethyl)benzoyloxy)-3-(S)-(4-fluoro)phenyl-4-benzyl morpholine (Example 72) using a procedure analogous to Example 68.

Mass Spectrum (FAB): m/Z 526 (M+H, 75%), 270 (100%).

^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 2.42 (dt, J=3.6, 12.0), 2.90 (app d, J=12.0, 1H), 2.91 (d, J=13.6, 1H), 3.62–3.66 (m, 1H), 3.72 (d, J=2.6), 3.94 (d, J=13.6, 1H), 4.09 (dt, J=2.4, 12.0, 1H), 4.75 (d, J=3.2, 1H), 4.82 (d, J=3.2, 1H), 5.32 (d, J=2.6, 1H), 7.09 (t, J=8.8, 2H), 7.24–7.33 (m, 5H), 7.58–7.62 (m, 2H), 7.80 (s, 1H), 7.90 (s, 2H).

EXAMPLE 74

2-(R)-(1-(S)-(3,5-Bis(trifluoromethyl)phenyl) ethoxy)-3-(S)-(4-fluoro)phenyl morpholine and 2-(S)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl morpholine

A mixture of 1.83 g (3.5 mmol) of 2-(R)-(1-(3,5-bis (trifluoromethyl)phenyl)ethenyloxy)-3-(S)-(4-fluoro)

phenyl-4-benzyl morpholine (from Example 73) and 800 mg 5% rhodium on alumina catalyst in 40 mL of absolute ethanol was stirred under an atmosphere of hydrogen for 24 hours. The catalyst was filtered onto a pad of Celite; the reaction flask and filter cake were rinsed with 200 mL of ethyl acetate. The filtrate was concentrated in vacuo and the residue was pumped under high vacuum (1 mmHg, room temperature) to dryness.

The residue was redissolved in 40 mL of isopropanol; 800 mg of 10% palladium on carbon catalyst was added and the resulting mixture was stirred under an atmosphere of hydrogen for 24 hours. The catalyst was filtered onto a pad of Celite; the reaction flask and filter cake were rinsed with 200 mL of ethyl acetate. The filtrate was concentrated in vacuo. Flash chromatography on 50 g of silica gel using 2:1 v/v hexanes/ether, then 3:2 v/v ether/hexanes as the eluant afforded 283 mg of 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl) phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl morpholine and 763 mg of 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy) -3-(S)-(4-fluoro)phenyl morpholine, both as oils (total yield 68%).

For 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)ethoxy) -3-(S)-(4-fluoro)phenyl morpholine:

Mass Spectrum (FAB) m/Z 438 (M+H, 65%), 180 (100%).

^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 1.47 (d, J=6.8, 3H), 1.87 (br s, 1H), 3.03 (dd, J=2.8, 12.8), 3.17 (dt, J=4.0, 12.4, 1H), 3.43–3.47 (m, 1H), 3.80 (dt, J=3.2, 11.6), 4.10 (d, J=2.2, 1H), 4.70 (q, J=6.8, 1H), 4.87 (d, J=2.2, 1H), 6.99–7.03 (m, 2H), 7.23–7.27 (m, 2H), 7.63 (s, 2H), 7.66 (s, 1H).

For 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy) -3-(S)-(4-fluoro)phenyl morpholine:

Mass Spectrum (FAB) m/Z 438 (M+H, 75%), 180 (100%).

^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 1.16 (d, J=6.8), 1.80 (br s, 1H), 3.13 (dd, J=3.2, 12.4), 3.23 (dt, J=3.6, 12.4), 3.63 (dd, J=2.4, 11.2), 4.01 (d, J=2.4, 1H), 4.13 (dt, J=3.2, 12.0), 4.42 (d, J=2.4, 1H), 4.19 (q, J=6.8, 1H), 7.04–7.09 (m, 2H), 7.27–7.40 (m, 4H), 7.73 (s, 1H).

EXAMPLE 75

2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl) ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methylmorpholine

The title compound was prepared in 79% yield from 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S) -(4-fluoro)phenyl morpholine (from Example 74) using a procedure analogous to Example 70.

Mass Spectrum (FAB): m/Z 535 (M+H, 100%), 277 (60%).

^{1}H NMR ($CDCl_3$+CD_3OD, 400 MHz, ppm): δ 1.48 (d, J=6.8, 3H), 2.52 (app t, J=10.4, 1H), 2.85–2.88 (m, 2H), 3.47 (d, J=2.8, 1H), 3.63 (d, J=14.4, 1H), 3.70 (dd, J=2.0, 11.6, 1H), 4.24 (app t, J=10.8, 1H), 4.35 (d, J=2.8, 1H), 4.91 (q, J=6.8, 1H), 7.07 (app t, J=8.4, 2H), 7.15 (s, 2H), 7.37–7.40 (m, 2H), 7.65 (s, 1H).

Analysis Calcd for $C_{23}H_{21}F_7N_4O_3$: C, 51.69; H, 3.96; N, 10.48; F, 24.88. Found: C, 51.74; H, 4.04; N, 10.50; F, 24.59.

EXAMPLE 76

2-(R)-(1-(S)-(3,5-Bis(trifluoromethyl)phenyl) ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methylmorpholine

The title compound was prepared in 60% yield from 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl morpholine (from Example 74) using a procedure analogous to Example 70.

Mass Spectrum (FAB): m/Z 535 (M+H, 50%), 293 (100%).

^{1}H NMR ($CDCl_3$+CD_3OD, 400 MHz, ppm): δ 1.11 (d, J=6.4, 3H), 2.49 (dt, J=2.4, 11.2), 2.83 (app d, J=11.2, 1H), 2.95 (d, J=14.4, 1H), 2.48–2.58 (m, 3H), 3.99 (app t, J=9.6, 1H), 4.61 (q, J=6.4, 1H), 4.81 (d, J=2.4, 1H), 7.09 (t, J=8.8, 2H), 7.50–7.53 (m, 2H), 7.75 (app s, 3H), 10.40 (br s, 1H), 11.00 (br s, 1H).

EXAMPLE 77

2-(R)-(1-(R)-(3-(Trifluoromethyl)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo) methylmorpholine

Step A: 2-(R)-(1-(R)-(3-(Trifluoromethyl)phenyl) ethoxy)-3-(S)-phenyl morpholine

The title compound was prepared in 25% yield from 3-(S)-phenyl-4-benzyl-2-morpholinone (from Example 14) using procedures analogous to Examples 67–69.

^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 1.39 (d, J=6.6, 3H), 1.93 (br s, 1H), 3.10 (dd, J=3.0, 12.7, 1H), 3.20 (dt, J=3.6, 12.4, 1H), 3.58 (ddd, J=1.1, 3.8, 11.2, 1H), 4.00 (d, J=2.4, 1H), 4.12 (dt, J=3.0, 11.2, 1H), 4.44 (d, J=2.4, 1H), 4.79 (q, J=6.6, 1H), 6.72 (d, J=7.7, 1H), 7.01 (s, 1H), 7.09 (t, J=7.7, 1H), 7.18–7.25 (m, 2H), 7.25–7.3 (m, 3H), 7.34 (d, J=7.7, 1H). Analysis:

Calcd for $C_{19}H_{19}F_3N_1O_2$: C-65.14 H-5.47 N-4.00 F-16.27 Found: C-64.89 H-5.73 N-3.83 F-15.95

Step B: 2-(R)-(1-(R)-(3-(Trifluoromethyl)phenyl) ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo) methylmorpholine

The title compound was prepared in 90% yield from 2-(R)-(1-(R)-(3-(trifluoromethyl)phenyl)ethoxy)-3-(S)-phenyl morpholine (from Example 77, Step A) using a procedure analogous to Example 70.

^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 1.40 (d, J=6.3, 3H), 2.53 (br t, J=11.2, 1H), 2.86 (app d, J=12.2, 1H), 2.94 (d, J=14.3, 1H), 3.44 (br s, 1H), 3.63 (br d, J=14, 2H), 4.27 (app t, J=11.5, 1H), 4.34 (d, J=2.1, 1H), 4.76 (q, J=6.7, 1H), 6.63 (d, J=7.7, 1H), 6.93 (s, 1H), 7.06 (t, J=7.6, 1H), 7.25–7.45 (m, 6H), 9.63 (br s, 1H), 9.74 (br s, 1H).

Analysis: Calcd for $C_{22}H_{22}F_3N_4O_3$: C-59.06 H-4.96 N-12.52 F-12.74 Found: C-58.84 H-5.17 N-12.37 F-12.50

EXAMPLE 78

2-(R)-(1-(R)-(3-(Fluoro)-5-(trifluoromethyl)phenyl) ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo) methylmorpholine

Step A: 2-(R)-(1-(R)-(3-(Fluoro)-5-(trifluoromethyl) phenyl)ethoxy)-3-(S)-phenyl-morpholine

The title compound was prepared in 44% yield from 3-(S)-phenyl-4-benzyl-2-morpholinone (from Example 14) using procedures analogous to Examples 67–69.

^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 1.38 (d, J=6.6, 3H), 1.90 (br s, 1H), 3.17 (dd, J=3.0, 12.7, 1H), 3.18 (dt, J=3.6, 12.7, 1H), 3.58 (ddd, J=1.1, 3.8, 11.2, 1H), 4.02 (d, J=2.3, 1H), 4.11 (dt, J=3.0, 11.2, 1H), 4.44 (d, J=2.3, 1H), 4.78 (q, J=6.6, 1H), 6.29 (d, J=9.2, 1H), 6.85 (s, 1H), 7.03 (d, J=8.4, 1H), 7.18–7.26 (m, 2H), 7.26–7.3 (m, 3H).

Analysis: Calcd for $C_{19}H_{18}F_4N_1O_2$: C-61.95 H-4.93 N-3.80 F-20.63 Found: C-61.78 H-5.14 N-3.71 F-20.35

Step B: 2-(R)-(1-(R)-(3-(Fluoro)-5-(trifluoromethyl) phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methylmorpholine

The title compound was prepared in 77% yield from 2-(R)-(1-(R)-(3-(fluoro)-5-(trifluoromethyl)phenyl)ethoxy)-3-(S)-phenyl morpholine (from Example 78, Step A) using a procedure analogous to Example 70.

^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 1.40 (d, J=6.3, 3H), 2.54 (br t, J=11, 1H), 2.87 (app d, J=12, 1H), 2.94 (app d, J=14, 1H), 3.47 (br s, 1H), 3.63 (br t, J=14, 2H), 4.25 (app t, J=11, 1H), 4.35 (d, J=1.5, 1H), 4.75 (q, J=6.3, 1H), 6.62 (d, J=6.7, 1H), 6.78 (s, 1H), 7.01 (d J=8.4, 1H), 7.24 (d, J=3.9, 1H), 7.35 (br s, 4H), 9.61 (br s, 1H), 9.89 (br s, 1H).

Analysis: Calcd for $C_{22}H_{21}F_4N_4O_3$: C-56.77 H-4.55 N-12.04 F-16.33 Found: C-56.57 H-4.65 N-11.94 F-16.13

EXAMPLE 79

2-(S)-(3-Fluoro-5-trifluoromethyl)benzoyloxy)-3-(S) -(4-fluoro)phenyl-4-benzyl morpholine

The title compound was prepared in 57% yield from 3-(S)-(4-fluoro)phenyl-4-benzyl-2-morpholinone (from Example 59) using a procedure analogous to Example 67.

Mass Spectrum (CI): m/Z 478 (M+H, 100%)

^{1}H NMR ($CDCl_3$, 360 MHz, ppm): δ 2.50 (dt, J=3.3, 12.0, 1H), 2.96(d, J=12.0, 1H), 2.98 (d, J=13.6, 1H), 3.75 (dd,J= 1.7, 11.5, 1H), 3.80 (d, J=13.6, 1H), 3.75 (dd, J=1.7, 11.5, 1H), 3.80 (d, J=2.5, 1H), 3.92 (d, J=13.6, 1H), 4.19 (dt, J=2.1, 12.0, 1H), 6.20 (d,J=2.5, 1H), 6.99 (t, J=8.7, 2H), 7.2–7.37 (m, 5H), 7.51–7.55 (m, 3H), 7.89 (d, J=8.4, 1H), 8.09 (s, 1H).

EXAMPLE 80

2-(S)-(1-(3-Fluoro-5-trifluoromethyl)phenyl) ethenyloxy)-3-(S)-(4-fluoro)-phenyl-4-benzyl morpholine

The title compound was prepared in 85% yield from 2-(S)-(3-fluoro-5-trifluoromethyl)benzoyloxy)-3-(S)-(4-fluoro)phenyl-4-benzyl morpholine (from Example 79) using a procedure analogous to Example 68.

Mass Spectrum (CI): m/Z 476 (M+H, 100%)

^{1}H NMR ($CDCl_3$, 360 MHz, ppm): δ 2.42 (dt, J=3.6, 12.0 Hz, 1H), 2.90 (d, J=12.0, 1H), 2.91 (d, J=13.6, 1H), 3.60–3.62 (m, 1H), 3.72 (d, J=2.6, 1H), 3.92 (d, J=13.6, 1H), 4.09 (dt, J=2.4, 12.0, 1H), 4.67 (d, J=2.9, 1H) 4.76 (d, J=2.9, 1H), 5.28 (d, J=2.6, 1H), 7.07 (t, J=8.7, 2H), 7.2–7.37 (m, 7H), 7.53 (s, 1H), 7.57–7.61 (m, 2H).

EXAMPLE 81

2-(S)-(1-(S)-(3-Fluoro-5-trifluoromethyl)phenyl) ethoxy)-3-(S)-(4-fluoro)phenyl morpholine and 2-(S)-(1-(R)-(3-Fluoro-5-trifluoromethyl)phenyl) ethoxy)-3-(S)-(4-fluoro)phenyl morpholine

The title compounds were prepared from 2-(S)-(1-(3-fluoro-5-trifluoromethyl)phenyl)ethenyloxy)-3-(S)-(4-fluoro)-phenyl-4-benzyl morpholine (from Example 80) using a procedure analogous to Example 74, but using 10% palladium on charcoal as the catalyst.

For 2-(S)-(1-(S)-(3-Fluoro-5-trifluoromethyl)phenyl) ethoxy)-3-(S)-(4-fluoro)phenyl morpholine:

Mass Spectrum (CI): m/Z 388 (M+H, 100%)

^{1}H NMR ($CDCl_3$, 360 MHz, ppm): δ 1.12 (d, J=6.5, 1H),1.83 (s, 1H), 3.02 (d, J=10.1, 1H), 3.16 (dt, J=3.6,12.5, 1H), 3.43 (dd, J=2.7, 11.4, 1H), 3.81 (dt, J=2.9, 11.7, 1H), 4.09 (d, J=2.1, 1H), 4.62 (q, J=6.5, 1H), 4.84 (d, J=2.1, 1H), 7.05 (t, J=8.8, 2H), 7.2 (d, J=8.8, 2H), 7.32 (s, 1H), 7.38 (dd, J=5.5, 8.5, 2H).

For 2-(S)-(1-(R)-(3-Fluoro-5-trifluoromethyl)phenyl) ethoxy)-3-(S)-(4-fluoro)phenyl morpholine:

Mass Spectrum (CI): m/Z 387 (M^+, 100%)

^{1}H NMR ($CDCl_3$, 360 MHz, ppm): δ 1.42 (d, J=6.6, 3H), 1.91 (s, 1H), 3.11 (dd, J=3.2, 12.4, 1H), 3.22 (dt, J=3.6, 12.4, 1H), 3.58–3.62 (m, 1H), 4.01 (d, J=2.3, 1H), 4.11 (dt, J=3.2, 12.0, 1H), 4.41 (d, J=2.3, 1H), 4.80 (q, J=6.6, 1H), 6.41 (d, J=9.2, 1H), 6.86 (s, 1H), 7.02 (t, J=8.7, 2H), 7.08 (d, J=9.2, 2H), 7.21–7.26 (m, 2H).

EXAMPLE 82

2-(S)-(1-(R)-(3-Fluoro-5-trifluoromethyl)phenyl) ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl morpholine

The title compound was prepared from 2-(S)-(1-(R)-(3-fluoro-5-trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro) phenyl morpholine (from Example 81) using a procedure analogous to Example 70, mp 209°–211° C.

$[\alpha]_D$=+65.1 (c=1.0, methanol)

^{1}H NMR ($CDCl_3$, 360 MHz, ppm): δ 1.32 (d, J=6.4, 1H), 2.38 (t, J=11.9, 1H), 2.76 (d, J=13.9, 1H), 2.84 (d, J=11.5, 1H), 3.32 (s, 1H), 3.40 (d, J=13.9, 1H), 3.49 (s, 1H), 3.61 (d, J=11.2, 1H), 4.11 (t, J=11.3, 1H), 4.8 (q, J=6.4, 1H), 6.57 (d, J=9.4, 1H), 6.94 (s, 1H), 7.1 (t, J=8.7, 2H), 7.39 (d, J=8.7, 2H), 7.51 (s, 2H), 11.26 (s, 1H), 11.38 (s, 1H).

EXAMPLE 83

2-(S)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl) ethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl morpholine

Step A: N,N-Diacetyl-4-bromomethyl-2-imidazolone

The title compound was prepared according to the procedure of Dolan and Dushinsky (*Journal of the American Chemical Society*, 70, 657 (1948)).

Step B: 2-(S)-(1-(R)-(3,5-Bis(trifluoromethyl) phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methylmmorpholine

A mixture of 1.00 g (2.28 mmol) of 2-(S)-(1-(R)-(3,5-bis (trifluoro-methyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl morpholine (from Example 74), 0.62 g (2.40 mmol) of N,N-diacetyl-4-bromomethyl-2-imidazolone (from Example 83, Step A) and 0.63 g (4.56 mmol) of potassium carbonate in 10 mL of N,N-dimethylformamide was stirred at room temperature for 15 minutes. The reaction was diluted with 100 mL of ethyl acetate and washed with water, saturated aqueous sodium chloride solution, dried over magnesium sulfate, and evaporated in vacuo. The resulting oil was dissolved in 10 mL of ethanol; the resulting solution was treated with 1.05 mL of 33% ethanolic methylamine solution and stirred at room temperature for 10 minutes. The reaction mixture was concentrated in vacuo to afford a solid. Recrystallisation from ethyl acetate/methanol afforded 0.63 g of the title compound, mp 192°–194° C.

^{1}H NMR (d6-DMSO, 360 MHz, ppm): δ 1.35 (d, J=6.5, 3H), 2.25 (dt, J=8.7, 1H), 2.60 (d, J=13.8, 1H), 2.89 (d, J=11.6, 1H), 3.28–3.36 (m, 2H), 3.62 (d, J=10.2, 1H), 4.1 (t, J=10.0, 1H), 4.31 (d, J=2.7, 1H), 4.92 (q, J=6.5, 1H), 5.97 (s, 1H), 7.06 (t, J=8.8, 2H), 7.36 (s, 2H), 7.65–7.85 (m, 2H), 7.84 (s, 1H), 9.58 (s, 1H), 9.8 (s, 1H).

EXAMPLE 84

2-(S)-(1-(R)-(3-Fluoro-5-(trifluoromethyl)phenyl) ethoxy-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl morpholine

The title compound was prepared from 2-(S)-(1-(R)-(3-fluoro-5-trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro) phenyl morpholine (from Example 82) using a procedure analogous to Example 83, mp 209°–210° C.

$[\alpha]_D$=+92.8 (c=1.0, methanol).

^{1}H NMR (d_6-DMSO, 360 MHz, ppm) δ 1.31 (d, J=6.5, 3H), 2.24 (dt, J=3.0, 11.9, 1H), 2.6 (d, J=13.9, 1H), 3.61 (d, J=11.2, 1H), 4.1 (t, J=11.0, 1H), 4.29 (d, J=2.3, 1H), 4.8 (q, J=6.5, 1H), 6.00 (s, 1H), 6.55 (d, J=9.3, 1H), 6.94 (s, 1H), 7.11 (t, J=8.7, 2H), 7.39 (d, J=8.4, 1H), 7.51 (s, 2H), 9.59 (s, 1H), 9.84 (s, 1H).

EXAMPLE 85

2-(S)-(1-(S)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy) -3-(R)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methylmorpholine

The title compound was prepared from (R)-(4-fluoro) phenylglycine using procedures analogous to Example 59, 67, 68, 69 and 70.

$[\alpha]_D$=–67.7 (c=0.7, MeOH, 20° C.)

EXAMPLE 86

The following compounds are prepared from 3-(S)-phenyl-4-benzyl-2-morpholinone (from Example 14) or 3-(S)-(4-fluoro)phenyl-4-benzyl-2-morpholinone (from Example 59) using procedures analogous to Examples 15, 67–69 and 74. The hydrogenation of the 1-(substituted-aryl) ethenyloxy intermediates may be done with 10% palladium on carbon (Example 70) or 5% rhodium on alumina catalyst (Example 74) to give rapid reduction of the enol ether. Removal of the 4-benzyl substituent may be done catalytically under extended hydrogenation with 10% palladium on carbon or 5% rhodium on alumina catalyst or (when dehalogenation or cleavage of the ether might occur) in a second step with 1-chloroethyl chloroformate as in Example 4, Step C.

1) 2-(R)-(1-(R)-(3-(chloro)-5-(trifluoromethyl)phenyl) ethoxy)-3-(S)-phenyl-morpholine;
2) 2-(R)-(1-(R)-(3,5-(dimethyl)phenyl)ethoxy)-3-(S)-phenyl-morpholine;
3) 2-(R)-(1-(R)-(3-(fluoro)-5-(methyl)phenyl)ethoxy)-3-(S) -phenyl-morpholine;
4) 2-(R)-(1-(R)-(3-(chloro)-5-(methyl)phenyl)ethoxy)-3-(S) -phenyl-morpholine;
5) 2-(R)-(1-(R)-(3-(bromo)-5-(methyl)phenyl)ethoxy)-3-(S) -phenyl-morpholine;
6) 2-(R)-(1-(R)-(3-(isopropoxy)phenyl)ethoxy)-3-(S)-phenyl-morpholine;
7) 2-(R)-(1-(R)-(3-(isopropoxy)-5-(trifluoromethyl)phenyl) ethoxy)-3-(S)-phenyl-morpholine;
8) 2-(R)-(1-(R)-(3-(chloro)-5-(isopropoxy)phenyl)ethoxy)-3-(S)-phenyl-morpholine;
9) 2-(R)-(1-(R)-(3-(fluoro)-5-(isopropoxy)phenyl)ethoxy)-3-(S)-phenyl-morpholine;
10) 2-(R)-(1-(R)-(3-(t-butyl)phenyl)ethoxy)-3-(S)-phenyl-morpholine;
11) 2-(R)-(1-(R)-(3-(t-butyl)-5-(chloro)phenyl)ethoxy)-3-(S)-phenyl-morpholine;
12) 2-(R)-(1-(R)-(3-(t-butyl)-5-(trifluoromethyl)phenyl) ethoxy)-3-(S)-phenyl-morpholine;
13) 2-(R)-(1-(R)-(3,5-(dimethyl)-4-(fluoro)phenyl)ethoxy)-3-(S)-phenyl-morpholine
14) 2-(R)-(1-(R)-(3,5-(dimethyl)-4-(chloro)phenyl)ethoxy)-3-(S)-phenyl-morpholine;
15) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-4-(fluoro) phenyl)ethoxy)-3-(S)-phenyl-morpholine;
16) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-4-(chloro) phenyl)ethoxy)-3-(S)-phenyl-morpholine;
17) 2-(R)-(1-(R)-(3,5-(dichloro)phenyl)ethoxy)-3-(S)-phenyl-morpholine;
18) 2-(R)-(1-(R)-(3,5-(difluoro)phenyl)ethoxy)-3-(S)-phenyl-morpholine;
19) 2-(R)-(1-(R)-(1-(naphthyl)ethoxy)-3-(S)-phenyl-morpholine;
20) 2-(R)-(1-(R)-(1-(4-(fluoro)naphthyl))ethoxy)-3-(S)-phenyl-morpholine;
21) 2-(R)-(1-(R)-(1-(3-(fluoro)naphthyl))ethoxy)-3-(S)-phenyl-morpholine;
22) 2-(R)-(1-(R)-(1-(3-(chloro)naphthyl))ethoxy)-3-(S)-phenyl-morpholine;
23) 2-(R)-(1-(R)-(1-(3-(methyl)naphthyl))ethoxy)-3-(S)-phenyl-morpholine;
24) 2-(R)-(1-(R)-(1-(3-(trifluoromethyl)naphthyl))ethoxy)-3-(S)-phenyl-morpholine;
25) 2-(S)-(2-fluoro-5-trifluoromethyl)benzyloxy-3-(S)-phenyl-morpholine;
26) 2-(S)-(2-fluoro-5-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro)phenyl-morpholine;
27) 2-(R)-(1-(R)-(2-fluoro-5-trifluoromethyl)phenylethoxy) -3-(S)-phenyl-morpholine;
28) 2-(R)-(1-(R)-(2-fluoro-5-trifluoromethyl)phenylethoxy) -3-(S)-(4-fluoro)phenyl-morpholine;
29) 2-(S)-(2-chloro-5-trifluoromethyl)benzyloxy-3-(S)-phenyl-morpholine;
30) 2-(S)-(2-chloro-5-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro)phenyl-morpholine;
31) 2-(R)-(1-(R)-(2-chloro-5-trifluoromethyl)phenylethoxy) -3-(S)-phenyl-morpholine;
32) 2-(R)-(1-(R)-(2-chloro-5-trifluoromethyl)phenylethoxy) -3-(S)-(4-fluoro)phenyl-morpholine;
33) 2-(S)-(3-methyl)benzyloxy-3-(S)-phenyl-morpholine;
34) 2-(S)-(3-methyl)benzyloxy-3-(S)-(4-fluoro)phenyl-morpholine;
35) 2-(R)-(1-(R)-(3-methyl)phenylethoxy)-3-(S)-phenyl-morpholine;
36) 2-(R)-(1-(R)-(3-methyl)phenylethoxy)-3-(S)-(4-fluoro) phenyl-morpholine;
37) 2-(S)-(3-bromo)benzyloxy-3-(S)-phenyl-morpholine;
38) 2-(S)-(3-bromo)benzyloxy-3-(S)-(4-fluoro)phenyl-morpholine;
39) 2-(R)-(1-(R)-(3-bromo)phenylethoxy)-3-(S)-phenyl-morpholine;
40) 2-(R)-(1-(R)-(3-bromo)phenylethoxy)-3-(S)-(4-fluoro) phenyl-morpholine;
41) 2-(S)-(3-chloro)benzyloxy-3-(S)-phenyl-morpholine;
42) 2-(S)-(3-chloro)benzyloxy-3-(S)-(4-fluoro)phenyl-morpholine;
43) 2-(R)-(1-(R)-(3-chloro)phenylethoxy)-3-(S)-phenyl-morpholine;
44) 2-(R)-(1-(R)-(3-chloro)phenylethoxy)-3-(S)-(4-fluoro) phenyl-morpholine;

45) 2-(S)-(3-trifluoromethyl)benzyloxy-3-(S)-phenyl-morpholine;
46) 2-(S)-(3-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro) phenyl-morpholine;
47) 2-(S)-(3-t-butyl)benzyloxy-3-(S)-phenyl-morpholine;
48) 2-(S)-(3-t-butyl)benzyloxy-3-(S)-(4-fluoro)phenyl-morpholine;
49) 2-(R)-(1-(R)-(3-(thiomethyl)phenyl)ethoxy)-3-(S)-phenyl-morpholine;
50) 2-(R)-(1-(R)-(3-(thiomethyl)-5-(trifluoromethyl) phenyl)ethoxy)-3-(S)-phenyl-morpholine;
51) 2-(R)-(1-(R)-(2,2-(dimethyl)-5-(thiomethyl)-2,3-dihydrobenzofuran-7-yl)ethoxy)-3-(S)-phenyl-morpholine;
52) 2-(R)-(1-(R)-(3,5-(dimethoxy)phenyl)ethoxy)-3-(S)-phenyl-morpholine;
53) 2-(R)-(1-(R)-(3-(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;
54) 2-(R)-(1-(R)-(3-(fluoro)-5-(trifluoromethyl)phenyl) ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;
55) 2-(R)-(1-(R)-(3-(chloro)-5-(trifluoromethyl)phenyl) ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;
56) 2-(R)-(1-(R)-(3,5-(dimethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;
57) 2-(R)-(1-(R)-(3-(fluoro)-5-(methyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;
58) 2-(R)-(1-(R)-(3-(chloro)-5-(methyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;
59) 2-(R)-(1-(R)-(3-(bromo)-5-(methyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;
60) 2-(R)-(1-(R)-(3-(isopropoxy)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;
61) 2-(R)-(1-(R)-(3-(isopropoxy)-5-(trifluoromethyl) phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;
62) 2-(R)-(1-(R)-(3-(chloro)-5-(isopropoxy)phenyl)ethoxy) -3-(S)-(4-fluoro)phenyl-morpholine;
63) 2-(R)-(1-(R)-(3-(fluoro)-5-(isopropoxy)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;
64) 2-(R)-(1-(R)-(3-(t-butyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;
65) 2-(R)-(1-(R)-(3-(t-butyl)-5-(chloro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;
66) 2-(R)-(1-(R)-(3-(t-butyl)-5-(trifluoromethyl)phenyl) ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;
67) 2-(R)-(1-(R)-(3,5-(dimethyl)-4-(fluoro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;
68) 2-(R)-(1-(R)-(3,5-(dimethyl)-4-(chloro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;
69) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-4-(fluoro) phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;
70) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-4-(chloro) phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;
71) 2-(R)-(1-(R)-(3,5-(dichloro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;
72) 2-(R)-(1-(R)-(3,5-(difluoro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;
73) 2-(R)-(1-(R)-(1-(naphthyl)ethoxy)-3-(S)-(4-fluoro) phenyl-morpholine;
74) 2-(R)-(1-(R)-(1-(4-(fluoro)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;
75) 2-(R)-(1-(R)-(1-(3-(fluoro)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;
76) 2-(R)-(1-(R)-(1-(3-(chloro)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;
77) 2-(R)-(1-(R)-(1-(3-(methyl)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;
78) 2-(R)-(1-(R)-(1-(3-(trifluoromethyl)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;
79) 2-(R)-(1-(R)-(3-(thiomethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;
80) 2-(R)-(1-(R)-(3-(thiomethyl)-5-(trifluoromethyl) phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;
81) 2-(R)-(1-(R)-(2,2-(dimethyl)-5-(thiomethyl)-2,3-dihydrobenzofuran-7-yl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;
82) 2-(R)-(1-(R)-(3,5-(dimethoxy)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;
83) 2-(R)-(1-(R)-(phenyl)ethoxy)-3-(S)-phenyl-morpholine;
84) 2-(R)-(1-(R)-(phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine;
85) 2-(R)-(1-(R)-(3-(fluoro)phenyl)ethoxy)-3-(S)-phenyl-morpholine;
86) 2-(R)-(1-(R)-(3-(fluoro)phenyl)ethoxy)-3-(S)-(4-fluoro) phenyl-morpholine;
87) 2-(R)-(1-(R)-(4-(fluoro)phenyl)ethoxy)-3-(S)-phenyl-morpholine;
88) 2-(R)-(1-(R)-(4-(fluoro)phenyl)ethoxy)-3-(S)-(4-fluoro) phenyl-morpholine;
89) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(3-fluoro)phenyl-morpholine;
90) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(3,4-difluoro)phenyl-morpholine;
91) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(3,4-dichloro)phenyl-morpholine;
92) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(3,4-dimethyl)phenyl-morpholine;
93) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-3,4-methylenedioxyphenyl-morpholine;
94) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(2-naphthyl)-morpholine.

EXAMPLE 87

The following compounds are prepared from the corresponding 2-(S)-(substituted-benzyloxy)-3-(S)-aryl morpholines or 2-(R)-(1-(R)-(substituted-aryl)ethoxy)-3-(S)-aryl morpholines (from Example 86) using procedures analogous to Examples 17, 18, 36, 38, 83 or, in the case of the 4-(5-tetrazolyl)methyl-substituted morpholines, by alkylation of the morpholine (from Example 86) with chloroacetonitrile in the presence of a tertiary amine base in acetonitrile, followed by formation of the final product by reacting the resulting nitrile with either sodium azide or trimethylsilylazide in an appropriate solvent.

1) 2-(R)-(1-(R)-(3-(Chloro)-5-(trifluoromethylphenyl) ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
2) 2-(R)-(1-(R)-(3,5-(Dimethyl)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
3) 2-(R)-(1-(R)-(3-(Fluoro)-5-(methyl)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
4) 2-(R)-(1-(R)-(3-(Chloro)-5-(methyl)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
5) 2-(R)-(1-(R)-(3-(Bromo)-5-(methyl)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
6) 2-(R)-(1-(R)-(3-(Isopropoxy)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
7) 2-(R)-(1-(R)-(3-(Isopropoxy)-5-(trifluoromethyl)phenyl) ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
8) 2-(R)-(1-(R)-(3-(Chloro)-5-(isopropoxy)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
9) 2-(R)-(1-(R)-(3-(Fluoro)-5-(isopropoxy)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

10) 2-(R)-(1-(R)-(1-(3-(trifluoromethyl)naphthyl))ethoxy)-3-(S)-phenyl-4-(3-(-1,2,4-triazolo)methyl-morpholine;
11) 2-(R)-(1-(R)-(3-(t-Butyl)-5-(chloro)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
12) 2-(R)-(1-(R)-(3-(t-Butyl)-5-(trifluoromethyl)phenyl) ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
13) 2-(R)-(1-(R)-(3,5-(Dimethyl)-4-(fluoro)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
14) 2-(R)-(1-(R)-(3,5-(Dimethyl)-4-(chloro)phenyl)ethoxy) -3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
15) 2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)-4-(fluoro) phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo) methyl-morpholine;
16) 2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)-4-(chloro) phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo) methyl-morpholine;
17) 2-(R)-(1-(R)-(3,5-(Dichloro)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
18) 2-(R)-(1-(R)-(3,5-(Difluoro)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
19) 2-(R)-(1-(R)-(1-(Naphthyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
20) 2-(R)-(1-(R)-(1-(4-(Fluoro)naphthyl))ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
21) 2-(R)-(1-(R)-(1-(3-(Fluoro)naphthyl))ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
22) 2-(R)-(1-(R)-(1-(3-(Chloro)naphthyl))ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
23) 2-(R)-(1-(R)-(1-(3-(Methyl)naphthyl))ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
24) 2-(R)-(1-(R)-(1-(3-(Trifluoromethyl)naphthyl))ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
25) 2-(S)-(2-Fluoro-5-trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;
26) 2-(S)-(2-Fluoro-5-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;
27) 2-(R)-(1-(R)-(2-Fluoro-5-trifluoromethyl) phenylethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;
28) 2-(R)-(1-(R)-(2-Fluoro-5-trifluoromethyl) phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;
29) 2-(S)-(2-Fluoro-5-trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
30) 2-(S)-(2-Fluoro-5-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
31) 2-(R)-(1-(R)-(2-Fluoro-5-trifluoromethyl) phenylethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo) methyl-morpholine;
32) 2-(R)-(1-(R)-(2-chloro-5-trifluoromethyl)phenylethoxy) -3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo) methyl-morpholine;
33) 2-(S)-(2-Fluoro-5-trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl-morpholine;
34) 2-(S)-(2-Fluoro-5-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl-morpholine;
35) 2-(R)-(1-(R)-(2-Fluoro-5-trifluoromethyl) phenylethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo) methyl-morpholine;
36) 2-(R)-(1-(R)-(2-Fluoro-5-trifluoromethyl) phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl-morpholine;
37) 2-(S)-(2-Fluoro-5-trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(2-imidazolo)methyl-morpholine;
38) 2-(S)-(2-Fluoro-5-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(2-imidazolo)methyl-morpholine;
39) 2-(R)-(1-(R)-(2-Fluoro-5-trifluoromethyl) phenylethoxy)-3-(S)-phenyl-4-(2-imidazolo)methyl-morpholine;
40) 2-(R)-(1-(R)-(2-Fluoro-5-trifluoromethyl) phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(2-imidazolo) methyl-morpholine;
41) 2-(S)-(2-Fluoro-5-trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(4-imidazolo)methyl-morpholine;
42) 2-(S)-(2-Fluoro-5-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(4-imidazolo)methyl-morpholine;
43) 2-(R)-(1-(R)-(2-Fluoro-5-trifluoromethyl) phenylethoxy)-3-(S)-phenyl-4-(4-imidazolo)methyl-morpholine;
44) 2-(R)-(1-(R)-(2-Fluoro-5-trifluoromethyl) phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-imidazolo) methyl-morpholine;
45) 2-(S)-(2-Fluoro-5-trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(5-tetrazolo)methyl-morpholine;
46) 2-(S)-(2-Fluoro-5-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(5-tetrazolo)methyl-morpholine;
47) 2-(R)-(1-(R)-(2-Fluoro-5-trifluoromethyl) phenylethoxy)-3-(S)-phenyl-4-(5-tetrazolo)methyl-morpholine;
48) 2-(R)-(1-(R)-(2-Fluoro-5-trifluoromethyl) phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(5-tetrazolo) methyl-morpholine;
49) 2-(S)-(2-Fluoro-5-trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;
50) 2-(S)-(2-Fluoro-5-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;
51) 2-(R)-(1-(R)-(2-Fluoro-5-trifluoromethyl) phenylethoxy)-3-(S)-phenyl-4-(2-oxo-5H-pyrrol-4-yl) methyl-morpholine;
52) 2-(R)-(1-(R)-(2- Fluoro-5-trifluoromethyl) phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;
53) 2-(S)-(2-Chloro-5-trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;
54) 2-(S)-(2-Chloro-5-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;
55) 2-(R)-(1-(R)-(2-Chloro-5-trifluoromethyl) phenylethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;
56) 2-(R)-(1-(R)-(2-Chloro-5-trifluoromethyl) phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;
57) 2-(S)-(2-Chloro-5-trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
58) 2-(S)-(2-Chloro-5-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
59) 2-(R)-(1-(R)-(2-Chloro-5-trifluoromethyl) phenylethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo) methyl-morpholine;
60) 2-(R)-(1-(R)-(2-Chloro-5-trifluoromethyl) phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
61) 2-(S)-(2-Chloro-5-trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl-morpholine;
62) 2-(S)-(2-Chloro-5-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl-morpholine;

63) 2-(R)-(1-(R)-(2-Chloro-5-trifluoromethyl) phenylethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo) methyl-morpholine;

64) 2-(R)-(1-(R)-(2-Chloro-5-trifluoromethyl) phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl-morpholine;

65) 2-(S)-(2-Chloro-5-trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(2-imidazolo)methyl-morpholine;

66) 2-(S)-(2-Chloro-5-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(2-imidazolo)methyl-morpholine;

67) 2-(R)-(1-(R)-(2-Chloro-5-trifluoromethyl) phenylethoxy)-3-(S)-phenyl-4-(2-imidazolo)methyl-morpholine;

68) 2-(R)-(1-(R)-(2-Chloro-5-trifluoromethyl) phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(2-imidazolo) methyl-morpholine;

69) 2-(S)-(2-Chloro-5-trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(4-imidazolo)methyl-morpholine;

70) 2-(S)-(2-Chloro-5-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(4-imidazolo)methyl-morpholine;

71) 2-(R)-(1-(R)-(2-Chloro-5-trifluoromethyl) phenylethoxy)-3-(S)-phenyl-4-(4-imidazolo)methyl-morpholine;

72) 2-(R)-(1-(R)-(2-Chloro-5-trifluoromethyl) phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-imidazolo) methyl-morpholine;

73) 2-(S)-(2-Chloro-5-trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(5-tetrazolo)methyl-morpholine;

74) 2-(S)-(2-Chloro-5-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(5-tetrazolo)methyl-morpholine;

75) 2-(R)-(1-(R)-(2-Chloro-5-trifluoromethyl) phenylethoxy)-3-(S)-phenyl-4-(5-tetrazolo)methyl-morpholine;

76) 2-(R)-(1-(R)-(2-Chloro-5-trifluoromethyl) phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(5-tetrazolo) methyl-morpholine;

77) 2-(S)-(2- Chloro-5-trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;

78) 2-(S)-(2-Chloro-5-trifluoromethyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;

79) 2-(R)-(1-(R)-(2-Chloro-5-trifluoromethyl) phenylethoxy)-3-(S)-phenyl-4-(2-oxo-5H-pyrrol-4-yl) methyl-morpholine;

80) 2-(R)-(1-(R)-(2-Chloro-5-trifluoromethyl) phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;

81) 2-(S)-(3-Methyl)benzyloxy-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

82) 2-(S)-(3-Methyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

83) 2-(R)-(1-(R)-(3-Methyl)phenylethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

84) 2-(R)-(1-(R)-(3-Methyl)phenylethoxy)-3-(S)-(4-fluoro) phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

85) 2-(S)-(3-Methyl)benzyloxy-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

86) 2-(S)-(3-Methyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

87) 2-(R)-(1-(R)-(3-Methyl)phenylethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

88) 2-(R)-(1-(R)-(3-Methyl)phenylethoxy)-3-(S)-(4-fluoro) phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

89) 2-(S)-(3-Methyl)benzyloxy-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl-morpholine;

90) 2-(S)-(3-Methyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl-morpholine;

91) 2-(R)-(1-(R)-(3-Methyl)phenylethoxy)-3-(S)-phenyl-4-(4-(2- oxo-1,3-imidazolo)methyl-morpholine;

92) 2-(R)-(1-(R)-(3-Methyl)phenylethoxy)-3-(S)-(4-fluoro) phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl-morpholine;

93) 2-(S)-(3-Methyl)benzyloxy-3-(S)-phenyl-4-(2-imidazolo)methyl-morpholine;

94) 2-(S)-(3-Methyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(2-imidazolo)methyl-morpholine;

95) 2-(R)-(1-(R)-(3-Methyl)phenylethoxy)-3-(S)-phenyl-4-(2-imidazolo)methyl-morpholine;

96) 2-(R)-(1-(R)-(3-Methyl)phenylethoxy)-3-(S)-(4-fluoro) phenyl-4-(2-imidazolo)methyl-morpholine;

97) 2-(S)-(3-Methyl)benzyloxy-3-(S)-phenyl-4-(4-imidazolo)methyl-morpholine;

98) 2-(S)-(3-Methyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(4-imidazolo)methyl-morpholine;

99) 2-(R)-(1-(R)-(3-Methyl)phenylethoxy)-3-(S)-phenyl-4-(4-imidazolo)methyl-morpholine;

100) 2-(R)-(1-(R)-(3-Methyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-imidazolo)methyl-morpholine;

101) 2-(S)-(3-Methyl)benzyloxy-3-(S)-phenyl-4-(5-tetrazolo)methyl-morpholine;

102) 2-(S)-(3-Methyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(5-tetrazolo)methyl-morpholine;

103) 2-(R)-(1-(R)-(3-Methyl)phenylethoxy)-3-(S)-phenyl-4-(5-tetrazolo)methyl-morpholine;

104) 2-(R)-(1-(R)-(3-Methyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(5-tetrazolo)methyl-morpholine;

105) 2-(S)-(3-Methyl)benzyloxy-3-(S)-phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;

106) 2-(S)-(3-Methyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;

107) 2-(R)-(1-(R)-(3-Methyl)phenylethoxy)-3-(S)-phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;

108) 2-(R)-(1-(R)-(3-Methyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;

109) 2-(S)-(3-Bromo)benzyloxy-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

110) 2-(S)-(3-Bromo)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

111) 2-(R)-(1-(R)-(3-Bromo)phenylethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

112) 2-(R)-(1-(R)-(3-Bromo)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

113) 2-(S)-(3-Bromo)benzyloxy-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

114) 2-(S)-(3-Bromo)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

115) 2-(R)-(1-(R)-(3-Bromo)phenylethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

116) 2-(R)-(1-(R)-(3-Bromo)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

117) 2-(S)-(3-Bromo)benzyloxy-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl-morpholine;

118) 2-(S)-(3-Bromo)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl-morpholine;

119) 2-(R)-(1-(R)-(3-Bromo)phenylethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl-morpholine;

120) 2-(R)-(1-(R)-(3-Bromo)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl-morpholine;

121) 2-(S)-(3-Bromo)benzyloxy-3-(S)-phenyl-4-(2-imidazolo)methyl-morpholine;

122) 2-(S)-(3-Bromo)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(2-imidazolo)methyl-morpholine;

123) 2-(R)-(1-(R)-(3-Bromo)phenylethoxy)-3-(S)-phenyl-4-(2-imidazolo)methyl-morpholine;
124) 2-(R)-(1-(R)-(3-Bromo)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(2-imidazolo)methyl-morpholine;
125) 2-(S)-(3-Bromo)benzyloxy-3-(S)-phenyl-4-(4-imidazolo)methyl-morpholine;
126) 2-(S)-(3-Bromo)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(4-imidazolo)methyl-morpholine;
127) 2-(R)-(1-(R)-(3-Bromo)phenylethoxy)-3-(S)-phenyl-4-(4-imidazolo)methyl-morpholine;
128) 2-(R)-(1-(R)-(3-Bromo)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-imidazolo)methyl-morpholine;
129) 2-(S)-(3-Bromo)benzyloxy-3-(S)-phenyl-4-(5-tetrazolo)methyl-morpholine;
130) 2-(S)-(3-Bromo)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(5-tetrazolo)methyl-morpholine;
131) 2-(R)-(1-(R)-(3-Bromo)phenylethoxy)-3-(S)-phenyl-4-(5-tetrazolo)methyl-morpholine;
132) 2-(R)-(1-(R)-(3-Bromo)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(5-tetrazolo)methyl-morpholine;
133) 2-(S)-(3-Bromo)benzyloxy-3-(S)-phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;
134) 2-(S)-(3-Bromo)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;
135) 2-(R)-(1-(R)-(3-Bromo)phenylethoxy)-3-(S)-phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;
136) 2-(R)-(1-(R)-(3-Bromo)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;
137) 2-(S)-(3-Chloro)benzyloxy-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;
138) 2-(S)-(3-Chloro)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;
139) 2-(R)-(1-(R)-(3-Chloro)phenylethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;
140) 2-(R)-(1-(R)-(3-Chloro)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;
141) 2-(S)-(3-Chloro)benzyloxy-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
142) 2-(S)-(3-Chloro)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
143) 2-(R)-(1-(R)-(3-Chloro)phenylethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
144) 2-(R)-(1-(R)-(3-Chloro)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
145)2-(S)-(3-Chloro)benzyloxy-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl-morpholine;
146) 2-(S)-(3-Chloro)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl-morpholine;
147) 2-(R)-(1-(R)-(3-Chloro)phenylethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl-morpholine;
148) 2-(R)-(1-(R)-(3-Chloro)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl-morpholine;
149) 2-(S)-(3-Chloro)benzyloxy-3-(S)-phenyl-4-(2-imidazolo)methyl-morpholine;
150) 2-(S)-(3-Chloro)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(2-imidazolo)methyl-morpholine;
151) 2-(R)-(1-(R)-(3-Chloro)phenylethoxy)-3-(S)-phenyl-4-(2-imidazolo)methyl-morpholine;
152) 2-(R)-(1-(R)-(3-Chloro)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(2-imidazolo)methyl-morpholine;
153) 2-(S)-(3-Chloro)benzyloxy-3-(S)-phenyl-4-(4-imidazolo)methyl-morpholine;
154) 2-(S)-(3-Chloro)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(4-imidazolo)methyl-morpholine;
155) 2-(R)-(1-(R)-(3-Chloro)phenylethoxy)-3-(S)-phenyl-4-(4-imidazolo)methyl-morpholine;
156) 2-(R)-(1-(R)-(3-Chloro)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-imidazolo)methyl-morpholine;
157) 2-(S)-(3-Chloro)benzyloxy-3-(S)-phenyl-4-(5-tetrazolo)methyl-morpholine;
158) 2-(S)-(3-Chloro)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(5-tetrazolo)methyl-morpholine;
159) 2-(R)-(1-(R)-(3-Chloro)phenylethoxy)-3-(S)-phenyl-4-(5-tetrazolo)methyl-morpholine;
160) 2-(R)-(1-(R)-(3-Chloro)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(5-tetrazolo)methyl-morpholine;
161) 2-(S)-(3-Chloro)benzyloxy-3-(S)-phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;
162) 2-(S)-(3-Chloro)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;
163) 2-(R)-(1-(R)-(3-Chloro)phenylethoxy)-3-(S)-phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;
164) 2-(R)-(1-(R)-(3-Chloro)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;
165) 2-(S)-(3-Trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methylmorpholine;
166) 2-(S)-(3-Trifluoromethyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;
167) 2-(R)-(1-(R)-(3-Trifluoromethyl)phenylethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;
168) 2-(R)-(1-(R)-(3-Trifluoromethyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;
169) 2-(S)-(3-Trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
170) 2-(S)-(3-Trifluoromethyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
171) 2-(R)-(1-(R)-(1-(3-(trifluoromethyl)naphthyl))ethoxy)-3-(S)-phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;
172) 2-(R)-(1-(R)-(3-Trifluoromethyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
173) 2-(S)-(3-Trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl-morpholine;
174) 2-(S)-(3-Trifluoromethyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl-morpholine;
175) 2-(R)-(1-(R)-(3-Trifluoromethyl)phenylethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl-morpholine;
176) 2-(R)-(1-(R)-(3-Trifluoromethyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl-morpholine;
177) 2-(S)-(3-Trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(2-imidazolo)methyl-morpholine;
178) 2-(S)-(3-Trifluoromethyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(2-imidazolo)methyl-morpholine;
179) 2-(R)-(1-(R)-(3-Trifluoromethyl)phenylethoxy)-3-(S)-phenyl-4-(2-imidazolo)methyl-morpholine;
180) 2-(R)-(1-(R)-(3-Trifluoromethyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(2-imidazolo)methyl-morpholine;
181) 2-(S)-(3-Trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(4-imidazolo)methyl-morpholine;
182) 2-(S)-(3-Trifluoromethyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(4-imidazolo)methyl-morpholine;
183) 2-(R)-(1-(R)-(3-Trifluoromethyl)phenylethoxy)-3-(S)-phenyl-4-(4-imidazolo)methyl-morpholine;
184) 2-(R)-(1-(R)-(3-Trifluoromethyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-imidazolo)methyl-morpholine;
185) 2-(S)-(3- Trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(5-tetrazolo)methyl-morpholine;
186) 2-(S)-(3-Trifluoromethyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(5-tetrazolo)methyl-morpholine;

187) 2-(R)-(1-(R)-(3-Trifluoromethyl)phenylethoxy)-3-(S)-phenyl-4-(5-tetrazolo)methyl-morpholine;
188) 2-(R)-(1-(R)-(3-Trifluoromethyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(5-tetrazolo)methyl-morpholine;
189) 2-(S)-(3-Trifluoromethyl)benzyloxy-3-(S)-phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;
190) 2-(S)-(3-Trifluoromethyl)benzyloxy-3-(S)-(4-fluoro) phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;
191) 2-(R)-(1-(R)-(3-Trifluoromethyl)phenylethoxy)-3-(S)-phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;
192) 2-(R)-(1-(R)-(3-Trifluoromethyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;
193) 2-(S)-(3-t-Butyl)benzyloxy-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;
194) 2-(S)-(3-t-Butyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;
195) 2-(R)-(1-(R)-(3-t-Butyl)phenylethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;
196) 2-(R)-(1-(R)-(3-t-Butyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;
197) 2-(S)-(3-t-Butyl)benzyloxy-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
198) 2-(S)-(3-t-Butyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
199) 2-(R)-(1-(R)-(3-t-Butyl)phenylethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
200) 2-(R)-(1-(R)-(3-t-Butyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
201) 2-(S)-(3-t-Butyl)benzyloxy-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl-morpholine;
202) 2-(S)-(3-t-Butyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl-morpholine;
203) 2-(R)-(1-(R)-(3-t-Butyl)phenylethoxy)-3-(S)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl-morpholine;
204) 2-(R)-(1-(R)-(3-t-Butyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-(2-oxo-1,3-imidazolo)methyl-morpholine;
205) 2-(S)-(3-t-Butyl)benzyloxy-3-(S)-phenyl-4-(2-imidazolo)methyl-morpholine;
206) 2-(S)-(3-t-Butyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(2-imidazolo)methyl-morpholine;
207) 2-(R)-(1-(R)-(3-t-Butyl)phenylethoxy)-3-(S)-phenyl-4-(2-imidazolo)methyl-morpholine;
208) 2-(R)-(1-(R)-(3-t-Butyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(2-imidazolo)methyl-morpholine;
209) 2-(S)-(3-t-Butyl)benzyloxy-3-(S)-phenyl-4-(4-imidazolo)methyl-morpholine;
210) 2-(S)-(3-t-Butyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(4-imidazolo)methyl-morpholine;
211) 2-(R)-(1-(R)-(3-t-Butyl)phenylethoxy)-3-(S)-phenyl-4-(4-imidazolo)methyl-morpholine;
212) 2-(R)-(1-(R)-(3-t-Butyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(4-imidazolo)methyl-morpholine;
213) 2-(S)-(3-t-Butyl)benzyloxy-3-(S)-phenyl-4-(5-tetrazolo)methyl-morpholine;
214) 2-(S)-(3-t-Butyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(5-tetrazolo)methyl-morpholine;
215) 2-(R)-(1-(R)-(3-t-Butyl)phenylethoxy)-3-(S)-phenyl-4-(5-tetrazolo)methyl-morpholine;
216) 2-(R)-(1-(R)-(3-t-Butyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(5-tetrazolo)methyl-morpholine;
217) 2-(S)-(3-t-Butyl)benzyloxy-3-(S)-phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;
218) 2-(S)-(3-t-Butyl)benzyloxy-3-(S)-(4-fluoro)phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;
219) 2-(R)-(1-(R)-(3-t-Butyl)phenylethoxy)-3-(S)-phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;
220) 2-(R)-(1-(R)-(3-t-Butyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(2-oxo-5H-pyrrol-4-yl)methyl-morpholine;
221) 2-(R)-(1-(R)-(3-(thiomethylphenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
222) 2-(R)-(1-(R)-(3-(thiomethylphenyl)ethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;
223) 2-(R)-(1-(R)-(3-(thiomethylphenyl)ethoxy)-3-(S)-phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;
224) 2-(R)-(1-(R)-(3-(thiomethyl-5-(trifluoromethyl) phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo) methyl-morpholine;
225) 2-(R)-(1-(R)-(3-(thiomethyl-5-(trifluoromethyl) phenyl)ethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo) methyl-morpholine;
226) 2-(R)-(1-(R)-(3-(thiomethyl-5-(trifluoromethyl) phenyl)ethoxy)-3-(S)-phenyl-4-(3-(2-oxo-1,3-imidazolo) methyl-morpholine;
227) 2-(R)-(1-(R)-(2,2-(dimethyl)-5-(thiomethyl)-2,3-dihydrobenzofuran-7-yl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
228) 2-(R)-(1-(R)-(2,2-(dimethyl)-5-(thiomethyl)-2,3-dihydrobenzofuran-7-yl)ethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;
229) 2-(R)-(1-(R)-(2,2-(dimethyl)-5-(thiomethyl)-2,3-dihydrobenzofuran-7-yl)ethoxy)-3-(S)-phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;
230) 2-(R)-(1-(R)-(3,5-(dimethoxy)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
231) 2-(R)-(1-(R)-(3,5-(dimethoxy)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;
232) 2-(R)-(1-(R)-(3,5-(dimethoxy)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;
233) 2-(R)-(1-(R)-(3-(fluoro)-5-(trifluoromethyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
234) 2-(R)-(1-(R)-(3-(fluoro)-5-(trifluoromethyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;
235) 2-(R)-(1-(R)-(3-(fluoro)-5-(trifluoromethyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;
236) 2-(R)-(1-(R)-(3-(chloro)-5-(trifluoromethyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
237) 2-(R)-(1-(R)-(3-(chloro)-5-(trifluoromethyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;
238) 2-(R)-(1-(R)-(3-(chloro)-5-(trifluoromethyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;
239) 2-(R)-(1-(R)-(3,5-(dimethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
240) 2-(R)-(1-(R)-(3,5-(dimethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;
241) 2-(R)-(1-(R)-(3,5-(dimethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;
242) 2-(R)-(1-(R)-(3-(fluoro)-5-(methyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;
243) 2-(R)-(1-(R)-(3-(fluoro)-5-(methyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

244) 2-(R)-(1-(R)-(3-(fluoro)-5-(methyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

245) 2-(R)-(1-(R)-(3-(chloro)-5-(methyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

246) 2-(R)-(1-(R)-(3-(chloro)-5-(methyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

247) 2-(R)-(1-(R)-(3-(chloro)-5-(methyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

248) 2-(R)-(1-(R)-(3-(bromo)-5-(methyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

249) 2-(R)-(1-(R)-(3-(bromo)-5-(methyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

250) 2-(R)-(1-(R)-(3-(bromo)-5-(methyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

251) 2-(R)-(1-(R)-(3-(isopropoxy)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

252) 2-(R)-(1-(R)-(3-(isopropoxy)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

253) 2-(R)-(1-(R)-(3-(isopropoxy)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

254) 2-(R)-(1-(R)-(3-(isopropoxy)-5-(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

255) 2-(R)-(1-(R)-(3-(isopropoxy)-5-(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

256) 2-(R)-(1-(R)-(3-(isopropoxy)-5-(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

257) 2-(R)-(1-(R)-(3-(chloro)-5-(isopropoxy)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

258) 2-(R)-(1-(R)-(3-(chloro)-5-(isopropoxy)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

259) 2-(R)-(1-(R)-(3-(chloro)-5-(isopropoxy)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

260) 2-(R)-(1-(R)-(3-(fluoro)-5-(isopropoxy)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

261) 2-(R)-(1-(R)-(3-(fluoro)-5-(isopropoxy)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

262) 2-(R)-(1-(R)-(3-(fluoro)-5-(isopropoxy)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

263) 2-(R)-(1-(R)-(3-(t-butyl)-5-(chloro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

264) 2-(R)-(1-(R)-(3-(t-butyl)-5-(chloro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

265) 2-(R)-(1-(R)-(3-(t-butyl)-5-(chloro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

266) 2-(R)-(1-(R)-(3-(t-butyl)-5-(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

267) 2-(R)-(1-(R)-(3-(t-butyl)-5-(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

268) 2-(R)-(1-(R)-(3-(t-butyl)-5-(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

269) 2-(R)-(1-(R)-(3,5-(dimethyl)-4-(fluoro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

270) 2-(R)-(1-(R)-(3,5-(dimethyl)-4-(fluoro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

271) 2-(R)-(1-(R)-(3,5-(dimethyl)-4-(fluoro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

272) 2-(R)-(1-(R)-(3,5-(dimethyl)-4-(chloro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

273) 2-(R)-(1-(R)-(3,5-(dimethyl)-4-(chloro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

274) 2-(R)-(1-(R)-(3,5-(dimethyl)-4-(chloro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

275) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-4-(fluoro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

276) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-4-(fluoro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

277) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-4-(fluoro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

278) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-4-(chloro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

279) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-4-(chloro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

280) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-4-(chloro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

281) 2-(R)-(1-(R)-(3,5-(dichloro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

282) 2-(R)-(1-(R)-(3,5-(dichloro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

283) 2-(R)-(1-(R)-(3,5-(dichloro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

284) 2-(R)-(1-(R)-(3,5-(difluoro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

285) 2-(R)-(1-(R)-(3,5-(difluoro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

286) 2-(R)-(1-(R)-(3,5-(difluoro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

287) 2-(R)-(1-(R)-(1-(naphthyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

288) 2-(R)-(1-(R)-(1-(naphthyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

289) 2-(R)-(1-(R)-(1-(naphthyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

290) 2-(R)-(1-(R)-(1-(4-(fluoro)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

291) 2-(R)-(1-(R)-(1-(4-(fluoro)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

292) 2-(R)-(1-(R)-(1-(4-(fluoro)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

293) 2-(R)-(1-(R)-(1-(3-(fluoro)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

294) 2-(R)-(1-(R)-(1-(3-(fluoro)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

295) 2-(R)-(1-(R)-(1-(3-(fluoro)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

296) 2-(R)-(1-(R)-(1-(3-(chloro)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

297) 2-(R)-(1-(R)-(1-(3-(chloro)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

298) 2-(R)-(1-(R)-(1-(3-(chloro)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

299) 2-(R)-(1-(R)-(1-(3-(methyl)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

300) 2-(R)-(1-(R)-(1-(3-(methyl)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

301) 2-(R)-(1-(R)-(1-(3-(methyl)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

302) 2-(R)-(1-(R)-(1-(3-(trifluoromethyl)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

303) 2-(R)-(1-(R)-(1-(3-(trifluoromethyl)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

304) 2-(R)-(1-(R)-(1-(3-(trifluoromethyl)naphthyl))ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

305) 2-(R)-(1-(R)-(3-(thiomethylphenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

306) 2-(R)-(1-(R)-(3-(thiomethylphenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

307) 2-(R)-(1-(R)-(3-(thiomethylphenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

308) 2-(R)-(1-(R)-(3-(thiomethyl-5-(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

309) 2-(R)-(1-(R)-(3-(thiomethyl-5-(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

310) 2-(R)-(1-(R)-(3-(thiomethyl-5-(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

311) 2-(R)-(1-(R)-(2,2-(dimethyl)-5-(thiomethyl)-2,3-dihydrobenzofuran-7-yl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

312) 2-(R)-(1-(R)-(2,2-(dimethyl)-5-(thiomethyl)-2,3-dihydrobenzofuran-7-yl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

313) 2-(R)-(1-(R)-(2,2-(dimethyl)-5-(thiomethyl)-2,3-dihydrobenzofuran-7-yl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

314) 2-(R)-(1-(R)-(3,5-(dimethoxy)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

315) 2-(R)-(1-(R)-(3,5-(dimethoxy)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

316) 2-(R)-(1-(R)-(3,5-(dimethoxy)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

317) 2-(R)-(1-(R)-(phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

318) 2-(R)-(1-(R)-(phenyl)ethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

319) 2-(R)-(1-(R)-(phenyl)ethoxy)-3-(S)-phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

320) 2-(R)-(1-(R)-(phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

321-2-(R)-(1-(R)-(phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

322) 2-(R)-(1-(R)-(phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

323) 2-(R)-(1-(R)-(3-(fluoro)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

324) 2-(R)-(1-(R)-(3-(fluoro)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

325) 2-(R)-(1-(R)-(3-(fluoro)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

326) 2-(R)-(1-(R)-(3-(fluoro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

327) 2-(R)-(1-(R)-(3-(fluoro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

328) 2-(R)-(1-(R)-(3-(fluoro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

329) 2-(R)-(1-(R)-(4-(fluoro)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

330) 2-(R)-(1-(R)-(4-(fluoro)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

331) 2-(R)-(1-(R)-(4-(fluoro)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

332) 2-(R)-(1-(R)-(4-(fluoro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

332) 2-(R)-(1-(R)-(4-(fluoro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

333) 2-(R)-(1-(R)-(4-(fluoro)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

334) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(3-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

335) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(3-fluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

336) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(3-fluoro)phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

337) 2-(R)2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(3,4-difluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

338) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(3,4-difluoro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

339) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(3,4-difluoro)phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

340) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(3,4-dichloro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

341) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(3,4-dichloro)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

342) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(3,4-dichloro)phenyl-4-(3-(2-oxo-1,3-imidazolo) methyl-morpholine;

343) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(3,4-dimethyl)phenyl-4-(3-(5-oxo-1,2,4-triazolo) methyl-morpholine;

344) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(3,4-dimethyl)phenyl-4-(3-(1,2,4-triazolo)methyl-morpholine;

345) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(3,4-dimethyl)phenyl-4-(3-(2-oxo-1,3-imidazolo) methyl-morpholine;

346) 2-(R)-(1-(R)-(3,5-bis(trifluoromethhyl)phenyl)ethoxy) -3-(S)-3,4-methylenedioxyphenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine;

347) 2-(R)-(1-(R)-(3,5-bis(trifluoromethhyl)phenyl)ethoxy) -3-(S)-3,4-methylenedioxyphenyl-4-(3 o (1,2,4-triazolo) methyl-morpholine;

348) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-3,4-methylenedioxyphenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

349) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(2-naphthyl)-4-(3-(5- oxo-1,2,4-triazolo)methyl-morpholine;

350) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(2-naphthyl)-4-(3-(1,2,4-triazolo)methyl-morpholine;

351) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(2-naphthyl)4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

352) 2-(R)-(1-(R)-(3-(fluoro)-5-(trifluoromethyl)ethoxy)-3-(S)-phenyl-4-(3-(-1,2,4-triazolo)methyl-morpholine;

353) 2-(R)-(1-(R)-(3-(fluoro)-5-(trifluoromethyl)ethoxy)-3-(S)-phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

354) 2-(R)-(1-(R)-(3-(chloro)-5-(trifluoromethyl)ethoxy)-3-(S)-phenyl-4-(3-(-1,2,4-triazolo)methyl-morpholine;

355) 2-(R)-(1-(R)-(3-(chloro)-5-(trifluoromethyl)ethoxy)-3-(S)-phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

356) 2-(R)-(1-(R)-(3,5-(dimethyl)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(-1,2,4-triazolo)methyl-morpholine;

357) 2-(R)-(1-(R)-(3,5-(dimethyl)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

358) 2-(R)-(1-(R)-(3-(fluoro)-5-(methyl)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(-1,2,4-triazolo)methyl-morpholine;

359) 2-(R)-(1-(R)-(3-(fluoro)-5-(methyl)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

360) 2-(R)-(1-(R)-(3-(chloro)-5-(methyl)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(-1,2,4-triazolo)methyl-morpholine;

361) 2-(R)-(1-(R)-(3-(chloro)-5-(methyl)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

362) 2-(R)-(1-(R)-(3-(bromo)-5-(methyl)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(-1,2,4-triazolo)methyl-morpholine;

363) 2-(R)-(1-(R)-(3-(bromo)-5-(methyl)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

364) 2-(R)-(1-(R)-(3-(isopropoxy)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(-1,2,4-triazolo)methyl-morpholine;

365) 2-(R)-(1-(R)-(3-(isopropoxy)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

366) 2-(R)-(1-(R)-(3-(isopropoxy)-5-(trifluoromethyl) phenyl)ethoxy)-3-(S)-phenyl-4-(3-(-1,2,4-triazolo) methyl-morpholine;

367) 2-(R)-(1-(R)-(3-(isopropoxy)-5-(trifluoromethyl) phenyl)ethoxy)-3-(S)-phenyl-4-(3-(2-oxo-1,3-imidazolo) methyl-morpholine;

368) 2-(R)-(1-(R)-(3-(chloro)-5-(isopropoxy)phenyl) ethoxy)-3-(S)-phenyl-4-(3-(-1,2,4-triazolo)methyl-morpholine;

369) 2-(R)-(1-(R)-(3-(chloro)-5-(isopropoxy)phenyl) ethoxy)-3-(S)-phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

370) 2-(R)-(1-(R)-(3-(fluoro)-5-(isopropoxy)phenyl) ethoxy)-3-(S)-phenyl-4-(3-(-1,2,4-triazolo)methyl-morpholine;

371) 2-(R)-(1-(R)-(3-(fluoro)-5-(isopropoxy)phenyl) ethoxy)-3-(S)-phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

372) 2-(R)-(1-(R)-(3-(t-butyl)-5-(chloro)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(-1,2,4-triazolo)methyl-morpholine;

373) 2-(R)-(1-(R)-(3-(t-butyl)-5-(chloro)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

374) 2-(R)-(1-(R)-(3-(t-butyl)-5-(trifluoromethyl)phenyl) ethoxy)-3-(S)-phenyl-4-(3-(-1,2,4-triazolo)methyl-morpholine;

375) 2-(R)-(1-(R)-(3-(t-butyl)-5-(trifluoromethyl)phenyl) ethoxy)-3-(S)-phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

376) 2-(R)-(1-(R)-(3,5-(dimethyl)-4-(fluoro)phenyl)ethoxy) -3-(S)-phenyl-4-(3-(-1,2,4-triazolo)methyl-morpholine;

377) 2-(R)-(1-(R)-(3,5-(dimethyl)-4-(fluoro)phenyl)ethoxy) -3-(S)-phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

378) 2-(R)-(1-(R)-(3,5-(dimethyl)-4-(chloro)phenyl)ethoxy) -3-(S)-phenyl-4-(3-(-1,2,4-triazolo)methyl-morpholine;

379) 2-(R)-(1-(R)-(3,5-(dimethyl)-4-(chloro)phenyl)ethoxy) -3-(S)-phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

380) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-4-(fluoro) phenyl)ethoxy)-3-(S)-phenyl-4-(3-(-1,2,4-triazolo) methyl-morpholine;

381) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-4-(fluoro) phenyl)ethoxy)-3-(S)-phenyl-4-(3-(2-oxo-1,3-imidazolo) methyl-morpholine;

382) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-4-(chloro) phenyl)ethoxy)-3-(S)-phenyl-4-(3-(-1,2,4-triazolo) methyl-morpholine;

383) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-4-(chloro) phenyl)ethoxy)-3-(S)-phenyl-4-(3-(2-oxo-1,3-imidazolo) methyl-morpholine;

384) 2-(R)-(1-(R)-(3,5-(dichloro)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(-1,2,4-triazolo)methyl-morpholine;

385) 2-(R)-(1-(R)-(3,5-(dichloro)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

386) 2-(R)-(1-(R)-(3,5-(difluoro)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(-1,2,4-triazolo)methyl-morpholine;

387) 2-(R)-(1-(R)-(3,5-(difluoro)phenyl)ethoxy)-3-(S)-phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

388) 2-(R)-(1-(R)-(1-(naphthyl)ethoxy)-3-(S)-phenyl-4-(3-(-1,2,4-triazolo)methyl-morpholine;

389) 2-(R)-(1-(R)-(1-(naphthyl)ethoxy)-3-(S)-phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

390) 2-(R)-(1-(R)-(1-(4-(fluoro)naphthyl))ethoxy)-3-(S)-phenyl-4-(3-(-1,2,4-triazolo)methyl-morpholine;

391) 2-(R)-(1-(R)-(1-(4-(fluoro)naphthyl))ethoxy)-3-(S)-phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

392) 2-(R)-(1-(R)-(1-(3-(fluoro)naphthyl))ethoxy)-3-(S)-phenyl-4-(3-(-1,2,4-triazolo)methyl-morpholine;

393) 2-(R)-(1-(R)-(1-(3-(fluoro)naphthyl))ethoxy)-3-(S)-phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

394) 2-(R)-(1-(R)-(1-(3-(chloro)naphthyl))ethoxy)-3-(S)-phenyl-4-(3-(-1,2,4-triazolo)methyl-morpholine;

395) 2-(R)-(1-(R)-(1-(3-(chloro)naphthyl))ethoxy)-3-(S)-phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine;

396) 2-(R)-(1-(R)-(1-(3-(methyl)naphthyl))ethoxy)-3-(S)-phenyl-4-(3-(-1,2,4-triazolo)methyl-morpholine; and

397) 2-(R)-(1-(R)-(1-(3-(methyl)naphthyl))ethoxy)-3-(S)-phenyl-4-(3-(2-oxo-1,3-imidazolo)methyl-morpholine.

EXAMPLE 88

2-(R)-(2,5-Bis(trifluoromethyl)benzoyloxy)-3-(S)-(4-fluorophenyl)-4-benzyl-morpholine

The title compound was prepared from 3-(S)-(4-fluorophenyl)-4-benzyl-2-morpholinone (from Example 59) using a procedure analogous to Example 67.

Mass Spectrum (CI): m/Z 528 (M+H)

^{1}H NMR ($CDCl_3$, 360 MHz, ppm): δ 2.46 (dt, 1H), 2.90 (dd, 2H), 3.76 (dd, J=11.6, 2.0, 1H), 3.88 (d, J=13.6, 1H), 4.18 (t, 1H), 6.20 (d, J=2.8, 1H), 7.04 (d, J=8.4, 2H), 7.24–7.32 (m, 5H), 7.50, (m, 2H), 7.60 (s, 1H), 7.88 (dd, 2H).

EXAMPLE 89

2-(R)-(1-(2,5-Bis(trifluoromethyl)phenyl) ethenyloxy)-3-(S)-(4-fluorophenyl)-4-benzyl-morpholine

The title compound was prepared from 2-(R)-(2,5-bis (trifluoromethyl)benzoyloxy)-3-(S)-(4-fluorophenyl)-4-benzyl-morpholine (from Example 88) using a procedure analogous to Example 68.

^{1}H NMR ($CDCl_3$, 250 MHz, ppm): δ 2.30 (dt, J=3.5, 11.9, 1H), 2.74 (app d, J=9.4, 1H), 2.82 (d, J=13.5, 1H), 3.55–3.60 (m, 2H), 3.72 (d, J=13.5, 1H), 4.10 (dt, J=2.4, 11.7, 1H), 4.22 (d, J=2.7, 1H), 4.67 (d, J=2.8, 1H), 5.18 (d, J=2.8, 1H), 6.90 (t, J=8.7, 2H), 7.08 (s, 1H), 7.13–7.23 (m, 5H), 7.36 (dd, J=5.6, 8.7, 2H). 7.62 (d, J=8.4, 1H), 7.72 (d, J=8.4, 1H).

EXAMPLE 90

2-(R)-(1-(R)-(2,5-Bis(trifluoromethyl)phenyl) ethoxy)-3-(S)-(4-fluorophenyl)-morpholine

The title compound was prepared from 2-(R)-(1-(2,5-bis (trifluoromethyl)phenyl)ethenyloxy)-3-(S)-(4-fluorophenyl) -4-benzyl-morpholine (from Example 89) using a procedure analogous to Example 74.

Mass Spectrum (CI): m/Z 438 (M+H)

^{1}H NMR Spectrum (HCl salt, d_6-DMSO, 360 MHz, ppm): δ 1.47 (d, J=8.7, 3H), 3.88 (d, J=11.8, 1H), 4.20 (dt, J=3.7, 11.8, 1H), 4.50 (s, 1H), 4.58 (s, 1H), 5.17 (m, 1H), 7.04 (s, 1H), 7.23 (t, J=8.8, 2H), 7.55 (m, 2H), 7.77 (d, J=8.1, 1H), 7.88 (d, J=8.3, 1H), 10.1 (br s, 1H).

EXAMPLE 91

2-(R)-(1-(R)-(2,5-Bis(trifluoromethyl)phenyl) ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine

The title compound was prepared from 2-(R)-(1-(R)-(2,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-morpholine (from Example 90) using a procedure analogous to Example 70, mp 162°–168° C.

^{1}H NMR (d_6-DMSO, 360 MHz, ppm) δ 1.37 (d, J=6.4, 3H), 2.40 (dt, J=3.3, 11.9, 1H), 2.77 (d, J=14.0, 1H), 2.86 (d, J=11.5, 1H), 3.37 (d, J=14.4, 1H), 3.48 (d, J=2.7, 1H), 3.64 (d, J=11.0, 1H), 4.11 (t, J=9.8, 1H), 4.18 (d, J=2.8, 1H), 5.16 (q, J=6.2, 1H), 6.90 (s, 1H), 7.08 (t, J=8.8, 2H), 7.50 (br t, 1H), 7.74 (d, J=8.3, 1H), 7.85 (d, J=8.3, 1H), 11.25 s, 1H), 11.35 (s, 1H).

EXAMPLE 92

2-(R)-(1-(R)-(2,5-Bis(trifluoromethyl)phenyl) ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(1,2,4-triazolo) methyl)morpholine

The title compound was prepared from 2-(R)-(1-(R)-(2,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-morpholine (from Example 90) using a procedure analogous to Example 17, mp 98°–100° C. Mass Spectrum (CI): m/Z 519 (M+H)

^{1}H NMR (d_6-DMSO, 360 MHz, ppm): δ 1.36 (d, J=6.4, 3H), 2.46 (dt, J=3.26, 11.9, 1H), 2.89 (d, J=11.0, 1H), 3.16 (d, J=13.9, 1H), 3.57– 3.64 (m, 3H), 4.09 (t, J=10.5, 1H), 4.18 (d, J=2.6, 1H), 5.14 (q, J=6.4, 1H), 6.90 (s, 1H), 7.11 (t, J=8.7, 2H), 7.48 (m, 2H), 7.72 (d, J=8.3, 1H), 7.83 (d, J=8.3, 1H), 8.36 (br s), 13.8 (s, 1H).

EXAMPLE 93

2-(R)-(1-(R)-(2,5-Bis(trifluoromethyl)phenyl) ethoxy)-3-(S)-(4-fluorophenyl)-4-(4-(2-oxo-1,3-imidazolo)methyl)morpholine

The title compound was prepared from 2-(R)-(1-(R)-(2,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-morpholine (from Example 90) using a procedure analogous to Example 83. A sample was recrystallized from aqueous ethanol, mp 203°–205° C.

^{1}H NMR (d_6-DMSO, 360 MHz, ppm): δ 1.35 (d, J=6.4, 3H), 2.25 (dt, J=3.1, 11.8, 1H), 2.58 (d, J=13.9, 1H), 2.88 (d, J=11.6, 1H), 3.24 (d, J=14.0, 1H), 3.35 (d, J=2.7, 1H), 3.64 (dd, J=9.6, 1H), 4.09 (t, J=9.8, 1H), 4.16 (d, J=2.7, 1H), 5.14 (q, J=6.5, 1H), 5.97 (s, 1H), 6.89 (s, 1H), 7.07 (t, J=8.7, 1H), 7.49 (m, 1H), 7.72 (d, J=8.1, 1H), 7.83 (d, J=8.3, 1H), 9.57 (s, 1H), 9.80 (s, 1H).

EXAMPLE 94

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl) morpholine N-oxide

A solution of 125 mg (0.25 mmol) of 2-(S)-(3,5-bis (trifluoromethyl)benzyloxy)-3-(S)-phenyl-4-(3-(5-oxo-1H, 4H-1,2,4-triazolo)methylmorpholine in 10 mL of methylene chloride was treated with 100 mg of 80–85% 3-chloroperoxybenzoic acid and the resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated in vacuo and the residue was partitioned between 25 mL of ethyl acetate and 25 mL of saturated aqueous sodium bicarbonate solution. The organic layer was separated, washed with 15 mL of 0.1N aqueous sodium hydroxide solution, dried over sodium sulfate and concentrated in vacuo to afford 142 mg of crude product. Flash chromatography on silica gel (15 mL column) using 95:5:0.5 v/v/v methylene chloride/methanol/water as the eluant afford 83 mg (64%) of the title compound. Mass Spectrum (NH_3-CI): m/Z 519 (20%, M^+), 406 (90%), 404 (100%).

^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 3.56–3.66 (m, 1H), 3.80 (br d, J=10.0, 1H), 3.95–4.20 (m, 3H), 4.43–4.47 (m, 1H), 4.50 (d, J=13.4, 1H), 4.86–4.94 (m, 3H), 7.32 (app s, 5H), 7.56 (s, 2H), 7.68 (s, 1H), 8.40 (br s, 1H) 12.15 (br s, 1H).

EXAMPLE 95

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-4-(3-(4-(ethoxycarbonyloxy-1-ethyl)5-oxo-1H,-1,2,4-triazolo)methyl)morpholine

A mixture of 250 mg (0.5 mmol) of 2-(S)-(3,5-bis (trifluoromethyl)benzyloxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,

4H-1,2,4-triazolo)methylmorpholine, 70 mg (0.5 mmol) of N,N-diisopropylethylamine and 100 mg (1-chloroethyl) ethylcarbonate in 15 mL of dichloroethane was heated at reflux for 16 hours. TLC analysis of the reaction mixture indicated incomplete reaction; the dichloroethane solvent was replaced with toluene, 70 mg of N,N-diisopropylethylamine and 100 mg (1-chloroethyl) ethylcarbonate were added to the reaction and the resulting mixture was heated at reflux for 24 hours. At this time, an additional 70 mg of N,N-diisopropylethylamine and 100 mg (1-chloroethyl)ethylcarbonate were introduced into the reaction and the resulting mixture was heated at reflux for 24 hours. The reaction was cooled to room temperature and partitioned between 25 mL of ethyl acetate and 25 mL of saturated aqueous sodium bicarbonate solution and the layers were separated. The aqueous layer was extracted with ethyl acetate. The organic layers were combined, dried over sodium sulfate and concentrated in vacuo to afford 420 mg of crude product as a foam. Flash chromatography on silica gel (25 mL column) using 100:1 v/v, then 50:1 v/v methylene chloride/isopropanol as the eluant afforded 68 mg (22%) of the title compound.

Mass Spectrum (ESI): m/Z 619 (15%, M+1), 575 (100%).

^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 1.38 (t, J=7.0, 3H), 2.61 (dt, J=3.0, 12.0, 1H), 2.90 (d, J=11.5, 1H), 3.03 (d, J=15.5, 1H), 3.63 (d, J=2.0, 1H), 3.66–3.71 (m, 2H), 4.20 (dt, J=2.0, 11.5, 1H), 4.41–4.45 (m, 2H), 4.48 (d, J=13.5, 1H), 4.71 (d, J=2.0, 1H), 4.81 (d, J=13.5, 1H), 7.34–7.48 (m, 5H), 7.47 (s, 2H), 7.72 (s, 1H), 10.1 (br s, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz, ppm): δ 14.2, 25.2, 50.7, 52.6, 59.2, 64.1, 64.5, 67.7, 69.7, 97.9, 121.5, 123.1 (q, J=271), 127.2, 128.7, 129.1, 131.5 (q, J=32.9), 136.0, 140.0, 146.8, 148.4, 152.3, 163.1.

EXAMPLE 96

2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl) ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(4-monophosphoryl-5-oxo-1H-1,2,4-triazolo)methyl) morpholine, dipotassium salt; or 2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(1-monophosphoryl-5-oxo-1H-1,2,4-triazolo)methyl)morpholine, dipotassium salt; or 2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(2-monophosphoryl-5-oxo-1H-1,2,4-triazolo)methyl)morpholine, dipotassium salt; or 2-(R)-(1-(R)-(3,5-Bis (trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(5-oxyphosphoryl-1H-1,2,4-triazolo) methyl)morpholine, dipotassium salt

A solution of 450 mg (0.84 mmol) of 2-(R)-(1-(R)-(3,5-bis(trifluoro-methyl)phenyl)ethoxy)-3-(S)-(4-fluoro) phenyl-4-(3-(5-oxo-1H,,4H-1,2,4-triazolo) methylmorpholine in 20 mL of THF at 0° C. was treated with 0.84 mL of 1.0M n-butyllithium solution in hexanes. The resulting solution was stirred cold for 5 minutes and was treated with 630 mg (1.17 mmol) of tetrabenzylpyrophosphate in one portion as a solid. The cooling bath was removed and the reaction was stirred at room temperature for 45 minutes. The reaction was quenched with 25 mL of saturated aqueous sodium bicarbonate solution and was extracted with 50 mL of ethyl ether. The organic layer was separated, washed with 25 mL of saturated aqueous sodium bicarbonate solution, 25 mL of 0.5N aqueous potassium hydrogen sulfate solution, 25 mL of saturated aqueous sodium chloride solution, dried over magnesium sulfate and concentrated in vacuo. The crude dibenzyl ester was dissolved in 25 mL of methanol. A solution of 168 mg (1.68 mmol) of potassium bicarbonate was added to the ester solution and the resulting mixture was hydrogenated at 40 psi in the presence of 45 mg of 10% palladium on carbon catalyst for 75 minutes. The catalyst was filtered onto a pad of Celite; the reaction flask and falter cake were rinsed well with methanol (~200 mL), the filtrate was concentrated in vacuo and dried. The residue was partially dissolved in methanol and filtered; the filtrate was concentrated and dried. The resulting solid was recrystallized from isopropanol to afford 280 mg of crude title compound. The solid was partitioned between 40 mL of ethyl ether and 20 mL of water; mixing of the layers resulted in an emulsion. Centrifugation at 2800 rpm for 15 minutes broke the emulsion; the aqueous layer was separated and lyophilized to afford 188 mg (33%) of the compound tentatively identified as 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(4-monophosphoryl-5-oxo-1H-1,2,4-triazolo)methyl)-morpholine, dipotassium salt as a solid.

^{1}H NMR (CD_3OD, 500 MHz, ppm): δ 1.43 (d, J=6.5, 3H), 2.45 (app t, J=8.5, 1H), 2.80 (d, J=14.0, 1H), 2.92 (d, J=11.5, 1H), 3.47–3.66 (m, 4H), 4.25 (app t, J=11.5, 1H), 4.36 (d, J=1.5, 1H), 4.94 (q, J=6.6, 1H), 7.05 (t, J=8.5, 2H), 7.31(s, 2H), 7.52 (br s, 2H), 7.71 (s, 1H).

^{13}C NMR (CD_3OD, 125 MHz, ppm): δ 24.7, 52.3, 53.4, 60.5, 70.6, 73.7, 97.2, 116.1 (d, J=21.9), 122.3, 124.6 (q, J=271.0), 127.7, 132.3, 132.6, 132.8, 134.3, 145.2 (d, J=11.0), 147.5, 159.0 (d, J=10.1), 164.0 (d, J=244.4).

EXAMPLE 97

2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)-phenyl) ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1-phosphoryl-5-oxo-4H-1,2,4-triazolo)methylmorpholine, bis(N-methyl-D-glucamine) salt

Tetrabenzylpyrophosphate was prepared in 71% yield using the procedure described by Khorana and Todd (*J. Chem. Soc.*,2257 (1953)). A solution of 2.00 g (3.7 mmol) of 2-(R)-(1-(R)-(3,5-bis(trifluormethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1H,4H-5-oxo-1,2,4-triazolo) methylmorpholine and 2.80 g (5.2 mmol) of tetrabenzylpyrophosphate in 50 mL of dry tetrahydrofuran was cooled to 0° C. A 1.0M solution of sodium bis(trimethylsilyl)-amide ("NaHMDS", 9.4 mL, 9.4 mmol) was added to the cooled reaction mixture using a syringe pump at a rate of 1 equivalent/hour maintaining the internal temperature at 0° C. After the addition of the NaHMDS, the reaction was stirred at 0° C. for 15 minutes and quenched with 100 mL of saturated aqueous sodium bicarbonate solution. The quenched mixture was extracted with 300 mL of ethyl ether; the ether extract was washed with 100 mL of 0.5N aqueous potassium bisulfate solution, 100 mL of saturated aqueous sodium bicarbonate solution, 100 mL of saturated aqueous sodium chloride solution, dried over magnesium sulfate and concentrated in vacuo.

A solution of the crude dibenzyl ester in 50 mL of methanol, a solution of 1.45 g (7.4 mmol) of N-methyl-D-glucamine in 10 mL of water and 200 mg of 10% palladium on carbon catalyst were combined and the mixture was hydrogenated at 40 psi for 2 hours. The reaction mixture was filtered through a pad of Celite; the reaction flask and filter cake were rinsed well with methanol (400 mL). The filtrate was concentrated in vacuo. The crude product was redissolved in 25 mL of methanol; 125 mL of isopropanol was added to the solution and the resulting mixture was aged at

room temperature for 30 minutes. The solid that had precipitated was filtered, washed with 75 mL of isopropanol. 75 mL of ethyl ether and air dried. The solid was partitioned between 150 mL of ethyl ether and 150 mL of water; an emulsion formed on mixing of the layers. The emulsion was transferred into 50 mL centrifuge tubes; centrifugation at 3000 rpm for 15 minutes caused separation of the layers. The organic layers were drawn off and the aqueous layers were combined, filtered and the filtrate lyophilized to afford 3.40 g of 2-(S)-(1-(R)-(3.5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1-phosphoryl-5-oxo-4H-1,2,4-triazolo)methylmorpholine, bis(N-methyl-D-glucamine) salt as an amorphous solid. Its purity was determined to be >99% by HPLC. ^{1}H NMR (CD_3OD, 500 MHz, ppm): δ 1.43 (d, J=6.6, 3H), 2.46 (app t, J=11.2, 1H), 2.72 (s, 6H), 2.84 (d, J=13.9, 1H), 2.94 (d, J=10.3, 1H), 3.12–3.30 (m, 4H), 3.42–3.83 (m, 14H), 4.19–4.25 (m, 3H), 4.35 (d, J=2.2, 1H), 7.04 (t, J=8.5, 2H), 7.30 (s, 2H), 7.52 (br s, 2H), 7.70 (s, 1H). ^{13}C NMR (CD_3OD, 125 MHz, ppm): δ 24.7, 34.4, 52.3, 53.1, 53.5, 60.5, 64.7, 69.9, 70.4, 72.0, 72.4, 72.6, 73.6, 97.1, 116.2 (d, J=21.9), 122.3, 124.5 (q, J=271.0), 127.7, 132.3, 132.7 (q, J=33.8), 134.2, 145.9, 147.5, 158.9, 163.9 (d, J=245.3).

EXAMPLE 98

4-Fluoro-α-[(phenylmethyl)amino]benzeneacetic acid

4-Fluorobenzaldehyde (7.0 kg, 56.4 moles) was added to a solution of sodium metabisulfite (5.76 kg, 30.3 moles) in water (50 L) and rinsed in with methanol (5 L). Sodium cyanide (2.83 kg, 57.7 moles) was added and rinsed in with water (3 L). The batch was stirred at 25° C. for 15 minutes before cooling to 8° C. A solution of benzylamine (6.04 kg, 56.4 moles) in methanol (11 L) was added. The batch was warmed to 34° C. and stirred for 2 hours. Water (23 L) was added and the batch was extracted with isopropyl acetate (30 L). The organic layer was washed with water (2×10 L) followed by saturated aqueous sodium chloride (10 L), then evaporated under reduced pressure to give a nitrile compound. The batch was dissolved in dimethylsulfoxide (50 L). Potassium carbonate (3.27 kg, 23.7 moles) was added and rinsed in with dimethylsulfoxide (6 L). Hydrogen peroxide solution in water (30%, 9.43 L, 83.2 moles) was added and the batch was stirred at room temperature overnight. The batch was diluted with water (120 L) and cooled to 13° C. The batch was filtered and the filter cake was washed with water (50 L). The resulting amide compound was dried on the filter, then slurried in industrial methylated spirits (38 L). A solution of sodium hydroxide pellets (3.27 kg, 81.75 moles) in water (11 L) was added to the batch and rinsed in with industrial methylated spirits (6 L).

After heating at reflux (80° C.) for 3.5 hours, the batch was distilled to low volume, removing the industrial methylated spirits. The batch was diluted with water (100 L) and extracted with isopropyl acetate (30 L). The layers were separated and the aqueous layer was acidified to pH 5–6 with concentrated hydrochloric acid. The precipitated solid was filtered and washed with water (2×10 L), then collected and dried under vacuum to give 12.3 kg (84% yield from 4-fluorobenzaldehyde) of 4-fluoro-α-[(phenylmethyl) amino]benzeneacetic acid.

EXAMPLE 99

4-Fluoro-α-[(phenylmethyl)amino]benzeneacetic acid methyl ester hydrochloride

4-Fluoro-α-[(phenylmethyl)amino]benzeneacetic acid (12.2 kg, 47.1 moles) was slurried in methanol (37 L), then hydrogen chloride gas was passed over the mixture. The resulting slurry was stirred at 35°–45° C. for 3 hours, then concentrated to 30–35 L by distillation. Methyl-t-butyl ether (20 L) was added and the batch was seeded with 4-Fluoro-α-[(phenylmethyl)amino]benzeneacetic acid methyl ester hydrochloride. Upon development of the seed-bed, methyl-t-butyl ether (20 L) was added. The slurry was aged for 1 hour, then filtered. The falter cake was washed with methyl-t-butyl ether:methanol (95:5, 8.0 L), then dried under vacuum at 30° C. to give 12.2 kg (84% yield) of 4-fluoro-α-[(phenylmethyl)amino]-benzeneacetic acid methyl ester hydrochloride.

EXAMPLE 100

α-Amino-4-fluorobenzeneacetic acid methyl ester

4-Fluoro-α-[(phenylmethyl)amino]benzeneacetic acid methyl ester hydrochloride (12.2 kg, 39.4 moles) was added to a slurry of 10% palladium-on-carbon (1.2 kg) in isopropanol (50 L). Ammonium formate (5.0 kg, 79.4 moles) was added and the batch was heated to 50° C. Progress of the reaction was monitored by HPLC. The batch was filtered through Hyflo Supercel and the filter cake was washed with isopropanol (25 L). The filtrate was evaporated to low volume and flushed with isopropyl acetate (50 L). The residue was dissolved in isopropyl acetate (30 L) and washed with 5% aqueous potassium phosphate (40 L), followed by saturated aqueous sodium chloride (10 L). The solution was evaporated under vacuum to give 5.79 kg (87% yield) of racemic α-amino-4-fluorobenzeneacetic acid methyl ester.

HPLC Conditions—Column: Zorbax Rx-C8, 25 cm×4.6 mm; Column temperature: 40° C.; Mobile phase: acetonitrile: 0.1% aqueous phosphoric acid (70:30 v/v); Flow rate: 1 mL/min; Detection: UV at 220 nm; Approximate retention times: α-amino-4-fluorobenzeneacetic acid methyl ester: 2.2 minutes; 4-fluoro-α-[(phenylmethyl)amino]benzeneacetic acid methyl ester 2.6 minutes. If unreacted 4-fluoro-α-[(phenylmethyl)amino]-benzeneacetic acid methyl ester (>2%) remains after 1 hour, a second charge of 10% palladium-on-carbon (300 g) slurried in isopropanol (2.0 L) can be made, followed by ammonium formate (1.0 kg). Heating then continues until the reaction is complete.

EXAMPLE 101

(S)-α-Amino-4-fluorobenzeneacetic acid

A solution of racemic α-amino-4-fluorobenzeneacetic acid methyl ester (3.32 kg, 18.2 moles) in 96% ethanol (5 L) was filtered then water (500 mL) was added to it. A solution of di-O-benzoyl-D-tartaric acid (DBT, 1.32 kg, 3.7 moles) in water:ethanol (1:7, 2.86 L) was then added. The crystallization mixture was cooled to 5° C. and aged for 1.5 hours. The product was collected by filtration, washed with water:ethanol (1:7, 1.1 L), air dried, then dried under vacuum at 50° C. to give 1.91 kg of α-amino-4-fluorobenzeneacetic acid methyl ester, DBT salt (95.8% ee).

Solvent (6.6 L) was removed from the liquors by evaporation under reduced pressure. Benzaldehyde (120 mL) was added and the solution was stirred and heated at 50° C. for 4 hours. The solution was filtered and the solids were washed with water:ethanol (1:7, 2×150 mL) (chiral HPLC showed the filtrate to contain racemic α-amino-4-fluorobenzeneacetic acid methyl ester). A solution of di-O-benzoyl-D-tartaric acid (439 g, 1.23 moles) in water:ethanol (1:7, 960 mL) was added to the filtrate, which was then was

cooled to 5° C. and aged for 1.5 hours. The product was collected by filtration, washed with water:ethanol (1:7, 2×1.1 L), air dried, then dried under vacuum at 50° C. to give 1.05 kg of α-amino-4-fluorobenzeneacetic acid methyl ester, DBT salt (95.4% ee). The combined yield of α-amino-4-fluorobenzeneacetic acid methyl ester, DBT salt was 2.96 kg (95% ee). The resolved α-amino-4-fluorobenzeneacetic acid methyl ester, DBT salt was partitioned between methyl-t-butyl ether (5 L) and 5.5M hydrochloric acid (6.2 L). The aqueous phase was washed with methyl-t-butyl ether (5 L), then filtered.

The α-amino-4-fluorobenzeneacetic acid methyl ester, DBT salt (2899 g, >95% ee) was partitioned between 5.5M hydrochloric acid (6.2 L) and the second methyl-t-butyl ether extract from above. The aqueous phase was re-extracted with methyl-t-butyl ether (5 L) and filtered. The aqueous filtrates were combined and concentrated by slow distillation of solvent. The batch was cooled and aged at 5° C. for 2 hours. The product was collected by filtration and air dried for 30 minutes to give 4.055 kg of (S)-α-amino-4-fluorobenzeneacetic acid, hydrochloride salt (98.7% ee). [(1)] Recrystallization from 5.5M hydrochloric acid (5 L) gave (S)-α-amino-4-fluorobenzeneacetic acid, hydrochloride salt as a wet cake (3.28 kg, 99.8% ee).

This wet cake was heated in a mixture of water (12 L) and concentrated hydrochloric acid (375 mL). Concentrated aqueous ammonia (1.2 L) and water (4 L) were added, then the batch was cooled to 20° C., and aged overnight. The product was collected by filtration, washed with water (6×4 L), air dried, then dried under vacuum at 50° C. for 24 hours to give 1.905 kg of (S)-α-amino-4-fluorobenzeneacetic acid free base (>99.7% ee, 48% yield from racemic α-amino-4-fluorobenzeneacetic acid methyl ester).

Chiral HPLC Conditions: Column: Crownpak CR(+), 15 cm×4.5 mm; Column temperature: 40° C.; Mobile phase: pH 2.0 aqueous perchloric acid:methanol (95:5 v/v); Flow rate: 1 mL/min; Detection: UV at 220 nm; Approximate retention times: (R)-α-Amino-4-fluorobenzeneacetic acid: 2.9 minutes; (S)-α-Amino-4-fluorobenzeneacetic acid: 5.6 minutes; (R) α-Amino-4-fluorobenzeneacetic acid methyl ester: 7.7 minutes; (S) α-Amino-4-fluorobenzeneacetic acid methyl ester: 14.0 minutes.

EXAMPLE 102

(S)-4-Fluoro-α-[(phenylmethyl)amino] benzeneacetate sodium salt

A solution of (S)-α-amino-4-fluorobenzeneacetic acid (1.00 kg, 5.91 moles) in aqueous sodium hydroxide (1M, 5.91 L) was filtered and added to 10% palladium-on-carbon (25 g). A solution of benzaldehyde (941 g, 8.87 moles) was added and the batch was stirred under hydrogen (50 psi) for 4 hours. The batch was filtered and the filtrate was evaporated to residue under vacuum, then flushed with ethanol (2×3 L). The residue was slurried in boiling ethanol (1.5 L), then cooled to 15° C. The slurry was filtered and the filter cake was washed with cold ethanol (2×500 mL), then dried under vacuum at 55° C. to give 1.83 kg (92% yield) of (S)-4-fluoro-α-[(phenylmethyl)-amino]benzeneacetate sodium salt.

EXAMPLE 103

(S)-3-(4-Fluoropheny)-4-(phenylmethyl)-2-morpholinone hydrochloride

(S)-4-Fluoro-α-[(phenylmethyl)-amino]benzeneacetate sodium salt (850 g, 3.02 moles) was added to 1,2-dibromoethane (4.85 kg, 25.8 moles) and diisopropylethylamine (419 g, 3.25 moles) in dimethylformamide (14.7 L). The batch was heated at 90° C. for 5 hours, then concentrated by distillation under vacuum to remove dimethylformamide. The residue was partitioned between ethyl acetate (3.2 L) and water (3.2 L). The aqueous layer was extracted with a second portion of ethyl acetate (2.0 L). The solution was dried over sodium sulfate, then filtered through a pad of silica (1.6 kg). The silica pad was rinsed with ethyl acetate (8.0 L) and the filtrate was evaporated under vacuum. The resulting residue was dissolved in a mixture of isopropanol (1.35 L) and ethyl acetate (400 mL), then filtered. A solution of hydrogen chloride gas in ethyl acetate (2.44M, 1.34 L) was added and the slurry was aged in an ice bath for 1 hour. The slurry was filtered and the filter cake was washed with 1:1 isopropanol:ethyl acetate (600 mL), followed by methyl-t-butyl ether (600 mL). The solid was dried under vacuum to give 749 g (77% yield, 98% ee) of (S)-3-(4-fluoropheny)-4-(phenylmethyl)-2-morpholinone hydrochloride.

Chiral HPLC Conditions: Column: Chiral (D)-Dinitrobenzoylphenylglycine (covalent) normal phase, 25 cm×4.6 mm; Column temperature: 35° C.; Mobile phase: hexane:ethanol (99:1 v/v); Flow rate: 1 mL/min; Detection: UV at 220 nm; Approximate retention times: (R)3-(4-Fluoropheny)-4-(phenylmethyl)-2-morpholinone: 16 minutes; (S)-3-(4-Fluoropheny)-4-(phenylmethyl)-2-morpholinone: 17 minutes.

EXAMPLE 104

Racemisation/Resolution of 3-(4-Fluorophenyl)-4-phenylmethyl-2-morpholinone

To a solution of 3-(4-fluorophenyl)-4-phenylmethyl-2-morpholinone (i.e. N-benzyl-4-fluorophenyl-1,4-oxazin-2-one) (10 g) in isopropyl acetate (110 ml) at room temperature was added a solution of (−)-3-bromocamphor-8-sulphonic acid ((−)-3BCS) (12 g) in acetonitrile (24 ml). Crystallisation began after 2–3 min. The slurry was stirred for 1 h at room temperature. Trifluoroacetic acid (7ml) was added and the mixture stirred at 65° C. for 3 days. The mixture was cooled to 0°–5° C., aged for 1 h. and the solid collected, washed with isopropyl acetate and dried in vacuo at 40° C., to give the N-benzyl-3-(S)-(4-fluorophenyl)-1,4-oxazin-2-one (−)-3BCS salt: yield 17.24 g, ee 98.6% (S) isomer. The chiral composition of the remaining liquors was determined as 79% (R), 21% (S). The liquors were stirred at 65° C. for 3 days, then cooled to 0°–5° C. The solid was collected, washed with isopropyl acetate and dried in vacuo to give a further batch of the N-benzyl-3-(S)-(4-fluorophenyl)-1,4-oxazin-2-one (−)-3BCS salt: yield 0.84 g, ee 98.6% (S) isomer. The chiral composition of the remaining liquors was determined as 64% (R), 36% (S). The liquors were stripped in vacuo and the residue was dissolved in isopropyl acetate (20 ml) containing trifluoroacetic acid (1 ml) and stirred at 65° C. for 20 h. The mixture was cooled to 0°–5° C. for 1 h and the solid collected, washed with isopropyl acetate and dried in vacuo to give a further batch of the N-benzyl-3-(S)-(4-fluorophenyl)-1,4-oxazin-2-one (−)-3BCS salt: yield 2.2 g, ee 99.2% (S) isomer. Total weight of (−)-3BCS salt: 20.28 g, 97% yield. A sample (0.5 g) of the (−)-3BCS salt was retained and the remainder converted back to free base. The salt was partitioned between isopropyl acetate (50 ml) and water (100 ml) containing 0.88 ammonia soln. (3 ml). The layers were separated and the aqueous phase extracted with isopropyl acetate (25 ml). The combined organic phases were washed with water (25 ml). The organic phase was concentrated to residue and flushed with

isopropyl acetate to give the 3-(S)-(4-fluorophenyl)-4-phenylmethyl-2-morpholinone (i.e. N-benzyl-3-(S)-(4-fluorophenyl)-1,4-oxazin-2-one) as the free base: yield 8.7 g, 93% recovery, ee 98.4% (S) isomer.

A further batch of N-benzyl-3-(S)-(4-fluorophenyl)-1,4-oxazin-2-one (−)-3BCS salt was prepared substantially according to the previous method except that the following quantities and reaction conditions were used: N-benzyl-3-(4-fluorophenyl)-1,4-oxazin-2-one (racemate) (4.96 g); (−)-3BCS in acetonitrile (1.85M; 9.4 ml); trifluoroacetic acid (2.1 ml); and isopropyl acetate (55 ml). The mixture was stirred at 90° C. for 6 days and then cooled to 0°–5° C. and aged for 1 hour. The solid N-benzyl-3-(S)-(4-fluorophenyl)-1,4-oxazin-2-one (−)-3BCS salt was collected and washed with isopropyl acetate (20 ml). Yield 9.40 g (90%); ee 99.6% (S) isomer. The chiral composition of the remaining liquors was determined as 88% (R), 12% (S).

EXAMPLE 105

(2R-cis)-3,5-bis(Trifluoromethyl)benzeneacetic acid 3-(4-fluorophenyl)-4-(phenylmethyl)-2-morpholinyl ester

A stirred suspension of (S)-3-(4-fluoropheny)-4-(phenylmethyl)-2-morpholinone hydrochloride (2.30 kg, 7.15 moles) in ethyl acetate (22 L) was treated with 10% aqueous sodium bicarbonate (22 L). The resulting organic solution was sequentially washed with 10% aqueous sodium bicarbonate (11 L) and water (2×11 L), then dried overnight with 4A molecular sieves (1 L). The solution was evaporated, then flushed with tetrahydrofuran (2×3 L) in order to remove traces of ethyl acetate. The resulting free base of (S)-3-(4-fluoropheny)-4-(phenylmethyl)-2-morpholinone was dissolved in tetrahydrofuran (19 L) and chilled to −75° C. L-Selectride (lithium tri-sec-butylborohydride, 6.74 L, 1.06M, 7.15 moles) was added to the batch while maintaining the temperature at less than −70° C. The batch was aged for 15 minutes, then 3,5-bis (trifluoromethyl)benzoyl chloride (2.57 kg, 9.29 moles) was added, maintaining the temperature at less than −70° C. The reaction was monitored by HPLC. The reaction was quenched with acetic acid (205 mL) in tetrahydrofuran (800 mL), and the batch was allowed to warm to ambient temperature overnight. The solution was vacuum concentrated and the resulting oil was diluted with hexanes (36 L). The batch was washed sequentially with water (17 L), 10% aqueous sodium bicarbonate (3×8.5 L), and water (2×8.5 L), then dried overnight using 4A molecular sieves (1 L). The batch was assayed by HPLC to contain 2.44 kg (65% yield) of (2R-cis)-3,5-bis(trifluoromethyl)benzeneacetic acid 3-(4-fluorophenyl)-4-(phenylmethyl)-2-morpholinyl ester. This batch was combined with another batch of (2R-cis)-3,5-bis (trifluoromethyl)benzeneacetic acid 3-(4-fluorophenyl)-4-(phenylmethyl)-2-morpholinyl ester (0.59 kg assay in 7 L hexanes) that was prepared just prior to the current batch. The combined batch solutions were filtered through a 20 μm line filter then diluted with hexanes (9 L). The crude (2R-cis)-3,5-bis(trifluoromethyl)benzeneacetic acid 3-(4-fluorophenyl)-4-(phenylmethyl)-2-morpholinyl ester solution (3.03 kg assay, 5.74 moles) was treated with hydrochloric acid in diethyl ether (9.6 L, 1.0M), giving a white precipitate of (2R-cis)-3,5-bis(trifluoromethyl) benzeneacetic acid 3-(4-fluorophenyl)-4-(phenylmethyl)-2-morpholinyl ester hydrochloride salt (the hydrochloride salt was formed in order to remove tri-sec-butyl borane residue (from the L-Selectride)). The solid was collected by filtration, washed with hexanes (2×8 L), then dried under nitrogen. The hydrochloride salt of the product was broken by slurrying in a mixture of toluene (36 L) and 10% aqueous sodium bicarbonate (13 L). The resulting organic solution was washed with 10% aqueous sodium bicarbonate (13 L) and water (2×18 L). The toluene solution was assayed to contain 3.00 kg of (2R-cis)-3,5-bis(trifluoromethyl)-benzeneacetic acid 3-(4-fluorophenyl)-4-(phenylmethyl)-2-morpholinyl ester (80% by area, corrected for toluene). The batch was stored over 4A molecular sieves (1 L).

HPLC conditions: Column: Zorbax RX-C8, 25 cm×4.6 mm; Mobile phase: acetonitrile: 0.1% aqueous phosphoric acid (75:25, v/v); Flow rate: 1.5 mL/min; Detection: UV at 220 nm Approximate retention times: Reduced (S)-3-(4-fluoropheny)-4-(phenylmethyl)-2-morpholinone: 1.6 minutes; (S)-3-(4-fluoropheny)-4-(phenylmethyl)-2-morpholinone: 3.3 minutes; (2R-cis)-3,5-bis (trifluoromethyl)-benzeneacetic acid 3-(4-fluorophenyl)-4-(phenylmethyl)-2-morpholinyl ester: 9.2 minutes.

EXAMPLE 106

(2R-cis)-2-[[1-[3.5-bis(Trifluoromethyl)phenyl] ethenyl]oxy]-3-(4-fluorophenyl)-4-(phenylmethyl) mopholine

A toluene solution of (2R-cis)-3,5-bis(trifluoromethyl)-benzeneacetic acid 3-(4-fluorophenyl)-4-(phenylmethyl)-2-morpholinyl ester (1.60 kg, 3.02 moles) was evaporated, then purged with nitrogen. Tetrahydrofuran (1.6 L) was added, followed by a solution of dimethyl titanocene in toluene (8.35 wt %, 1.73 kg of reagent, 8.31 moles) (prepared as noted below). The batch was sparged with nitrogen for 25 minutes, then heated to 80° C. The batch was aged in the dark for 5 hours at 80° C., then cooled to ambient temperature and aged overnight. The batch was solvent-switched to heptane by vacuum distillation, maintaining the temperature below 20° C. (126 L heptane added with concomitant distillation of 120 L) (the reaction mixture was solvent-switched to heptane and treated with bicarbonate buffered peroxide in order to precipitate the titanium residues). Water (22 L), sodium bicarbonate (2.0 kg), then 30% hydrogen peroxide (3.5 L) were added to the chilled (7° C.) mixture. The batch was stirred at ambient temperature overnight. The phases were partitioned, with much of the titanium residue remaining in the aqueous phase. The aqueous phase was back extracted with heptane (10 L), and the combined organic phases were filtered, washed with water (2×4 L), then concentrated. The crude product was recrystallized by dissolving in hot methanol (17 L), cooling to ambient temperature, then adding water (1.8 L). The material was isolated by filtration at 0° C. The filter cake was washed with 10% aqueous methanol (2 L, 0° C.), then the solid was dried at ambient temperature under nitrogen (1.45 kg of 94 wt % pure (2R-cis)-2-[[1-[3.5-bis(trifluoromethyl) phenyl]-ethenyl]oxy]-3-(4-fluorophenyl)-4-(phenylmethyl) mopholine, 85% yield).

The dimethyl titanocene reagent may be prepared as follows. Methyl lithium (590 g, 26.9 moles) in a solution of diethyl ether (4.38% w/w, 13.5 kg) was added to a chilled (−8° C.), well-stirred slurry of titanocene dichloride (3.35 kg, 13.5 moles) in methyl-t-butyl ether (13.4 L) while maintaining the temperature below 5° C. The resulting slurry was aged at 0°–5° C. for 1 hour. The reaction was quenched by adding water (8 L) while maintaining the temperature between 0° and 8° C. The organic phase was washed with cold water (4×3 L). The organic layer was then solvent-switched to toluene by distillation with concomitant addition of of toluene (24 L) while maintaining the temperature at 25°

C. or less. Weight percent assay by ^1H NMR showed the solution to contain 1.75 kg of dimethyl titanocene (63% yield. 8.35 wt % solution in toluene). The material was stored under nitrogen at 0° C. The progress of the reaction was followed by ^1H NMR (250 MHz, $CDCl_3$, 10 second delay between pulses). Cp_2TiMe_2: ∂ (ppm) 6.05 (s, 10H). –0.05 (s, 6H); $Cp_2TiClMe$: ∂ 6.22 (s, 10H). 0.80 (s, 3H); Cp_2TiCl_2: ∂ 6.56 (s, 10H).

Alternatively, the dimethyl titanocene reagent may be prepared as follows. To a well stirred slurry of titanocene dichloride (249 g, 1.00 mol) in toluene (2.75 L) chilled to –5° (internal temp) was added MeMgCl (750 mL, 3.0M in THF, 2.25 mol) over 1 h, maintaining the temperature below 8°. The resulting orange slurry is aged at 0°–5° for 1 h, or until the insoluble purple Cp_2TiCl_2 has dissolved. A NMR was taken to confirm reaction completion (see below), then the reaction was quenched into a solution of 6% aqueous ammonium chloride (700 mL), maintained at 0°–5°. The organic phase was washed with cold water (3×575 mL) and brine (575 mL), then was dried with Na_2SO_4 (220 g). The filtered organic layer was evaporated to 1.5 Kg (maintaining an internal temperature of 25° or less). Weight % assay by ^1H NMR showed the solution to contain 187 g product (90%, 12.5 wt % solution in toluene/THF). Typically, the material was greater than 95% pure, with only traces of the starting material and monomethyl intermediate. The solution may be further concentrated to 1.0 Kg, giving a 18 wt % solution in toluene, allowing for an easier assay. However, the presence of a small mount of THF increases the stability of the reagent. The material was stored under nitrogen in a sealed carboy at 0°. ^1H NMR Cp_2TiMe_2: δ 6.05 (s, 10H). –0.05 (s, 6H). $Cp_2TiClMe$: δ 6.22 (s, 10H). 0.80 (s, 3H). Cp_2TiCl_2: δ 6.56 (s, 10H). ^{13}C NMR Cp_2TiMe_2: δ 113.20 (Cp_2), 45.77 (Me_2). $Cp_2TiClMe$: δ 115.86 (Cp_2), 50.37 (Me). Cp_2TiCl_2: δ 120.18.

HPLC conditions: Column: Zorbax RX-C8, 25 cm×4.6 mm; Mobile phase: acetonitrile: 0.1% aqueous phosphoric acid (65:35, v/v); Flow rate: 1.5 mL/min; Detection: UV at 220 nm; Approximate retention times: (2R-cis)-2-[[1-[3.5-bis(Trifluoromethyl)phenyl]-ethenyl]oxy]-3-(4-fluorophenyl)-4-(phenylmethyl)mopholine: 17.2 minutes; (2R-cis)-3,5-bis(trifluoromethyl)-benzeneacetic acid 3-(4-fluorophenyl)-4-(phenylmethyl)-2-morpholinyl ester: 18.9 minutes.

The dimethyl titanocene reagent alternatively may be prepared as follows. To a well stirred slurry of titanocene dichloride (Cp_2TiCl_2) (6.0 g, 24.1 mmol) in toluene (72 mL) chilled to –5° C. was added dropwise methyl magnesium chloride (CH_3MgCl) (19.8 g, 19.2 mL, 3.0M in THF, 57.6 mmol, 2.4 eq) over 10 min, maintaining the temperature below 5° C. A viscous slurry was formed as magnesium chloride precipitated. The resulting slurry was aged at 0°–5° for 50 min, during which time the insoluble red Cp_2TiCl_2 had dissolved. A NMR assay on a quenched sample was taken to confirm reaction completion. A 0.2 mL sample was quenched into 1 mL of water and 1 ml of $CDCl_3$. The chloroform layer was used directly for NJR analysis. Dimethyl titanocene has resonances at 6.0 ppm (Cp) group and –0.2 ppm (CH_3 group). The monomethyl compound has resonances 0.2–0.3 ppm downfield, and the titanocene dichloride has resonance at 6.5 ppm.

The reaction was then quenched by addition of a solution of 10% aqueous ammonium chloride (20 mL) over 10 min, maintaining the temperature below 10° C. The layers were separated and the organic phase was washed with cold water (3×20 mL) and brine (20 mL), then was dried with Na2SO$_4$ (20 g). The filtered organic layer was concentrated under vacuum to approximately half volume. The total weight of the solution was 43 g, and NMR analysis showed 11.2 wt % in dimethyl titanocene (4.8 g, 96% yield). The THF level was 2%, however, the presence of a small amount of THF increases the stability of the reagent. The material was stored under nitrogen at 0° C.

The dimethyl titanocene reagent alternatively may also be prepared as follows. To a well stirred slurry of titanocene dichloride (Cp_2TiCl_2) (249 g, 1.00 mol) in toluene (2.75 L) chilled to –5° C. (internal temp) was added methyl magnesium chloride (CH_3MgCl) (750 mL, 3.0M in THF, 2.25 mol) over 1h, maintaining the temperature below 8° C. The resulting orange slurry is aged at 0°–5° C. for 1 h, or until the insoluble purple Cp_2TiCl_2 has dissolved. A NMR was taken to confirm reaction completion (see below), then the reaction was quenched into a solution of 6% aqueous ammonium chloride (700 mL), maintained at 0°–5° C. The layers were separated and the organic phase was washed with cold water (3×575 mL) and brine (575 mL), then was dried with Na_2SO_4 (220 g). The filtered organic layer was evaporated to 1.5 Kg (maintaining an internal temperature of 25° or less). Weight assay by ^1H NMR showed the solution to contain 187 g product (90%, 12.5 wt % solution in toluene/THF). Typically, the material was greater than 95% pure, with only traces of the starting material and monomethyl intermediate. The solution may be further concentrated to 1.0 Kg, giving a 18 wt % solution in toluene, allowing for an easier assay. However, the presence of a small mount of THF increases the stability of the compound. The material was stored under nitrogen in a sealed carboy at 0° C. ^1H NMR $Cp_2Ti(CH_3)_2$: δ 6.05 (s, 10H), –0.05 (s, 6H). $Cp_2TiCl(CH_3)$: δ 6.22 (s, 10H), 0.80 (s, 3H). Cp_2TiCl_2: δ 6.56 (s, 10H). ^{13}C NMR $Cp_2Ti(CH_3)_2$: δ 113.20 (Cp_2), 45.77 ($(CH_3)_2$). $Cp_2TiClCH_3$: δ 115.86 (Cp_2), 50.37 (CH_3). Cp_2TiCl_2: δ 120.18.

EXAMPLE 107

(2R-cis)-2-[[1-[3.5-bis(Trifluoromethyl)phenyl] ethenyl]oxy]-3-(4-fluorophenyl)-4-(phenylmethyl) mopholine

A toluene solution of (2R-cis)-3,5-bis(trifluoromethyl) benzeneacetic acid 3-(4-fluorophenyl)-4-(phenylmethyl)-2-morpholinyl ester [i.e. (4-benzyl-2-(R)-(3,5-bis (trifluoromethyl)benzoyloxy)-3-(S)-(4-fluorophenyl)-1,4-oxazine] solution contained 2.99 Kg, 5.67 mol) was evaporated into a 100 L flask. The flask was purged with nitrogen, then tetrahydrofuran (25 L) was added, followed by a solution of dimethyl titanocene in toluene/THF (12.5 wt %, 4.2 Kg contained reagent, 20.2 mol). The orange solution was sparged with nitrogen for 25 minutes, then was heated to 80° C. The reaction was aged in the dark for 4 h at 80° C., the was cooled to ambient temperature. Methanol (11.6 L) and water (1.9 L) was added and the mixture was heated at 40° C. overnight, precipitating the titanium residues as a green solid. After cooling to ambient temperature, the solid was removed by filtration, the filtercake washed with toluene, and the resulting mother liquors were evaporated. The crude product was recrystallized by dissolving in hot methanol (30 L), cooling to ambient temperature, then adding water (3.4 L) over 3 h. The material was isolated via filtration at 0° C., the filtercake was washed with 0° C. 10% aq. methanol (2 L), and the solid was dried at ambient temperature under nitrogen, 2.55 Kg of (2R-cis)-2-[[1-[3.5-bis(Trifluoromethyl)phenyl]ethenyl]oxy]-3-(4-fluorophenyl)-4-(phenylmethyl)mopholine (85%) was isolated.

EXAMPLE 108

[2R-[2a(R*),3a]]-2-[1-[3,5-bis(Trifluoromethyl) phenyl]ethoxy]-3-(4-fluorophenyl)morpholine 4-methylbenzenesulfonate (salt)

A solution of (2R-cis)-2-[[1-[3.5-bis(trifluoromethyl) phenyl]ethenyl]oxy]-3-(4-fluorophenyl)-4-(phenylmethyl) mopholine (1082 g, 94% pure, 1.94 moles) in 1:1 ethyl acetate:ethanol (13 L) was mixed with 10% palladium-on-carbon (165 g). The resulting slurry was treated with hydrogen (40 psi, 20°–25° C.) for 12 hours. The reaction was monitored by hydrogen uptake and HPLC. The vessel was vented, and the catalyst was removed by filtration. After washing the catalyst with 1:1 ethyl acetate:ethanol (6 L) followed by ethyl acetate (2 L), the combined organic phases containing crude [2R-[2a(R*),3a]]-2-[1-[3,5-bis (Trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl) morpholine were vacuum concentrated. A second batch, starting with 1078 g of (2R-cis)-2-[[1-[3.5-bis (trifluoromethyl)phenyl]ethenyl]oxy]-3-(4-fluorophenyl)-4-(phenylmethyl)mopholine (1.93 moles) was prepared. The resulting crude [2R-[2a(R*),3a]]-2-[1-[3,5-bis (trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl) morpholine was vacuum concentrated and combined with the first batch. The combined batches of crude [2R-[2a(R*) ,3a]]-2-[1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)morpholine were flushed with methyl-t-butyl ether (2×3 L) in order to remove residual ethyl acetate and ethanol, then were dissolved in methyl-t-butyl ether (3 L). The solution was assayed to contain 1348 g (3.09 moles, 80% yield) of [2R-[2a(R*),3a]]-2-[1-[3,5-bis (trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl) morpholine (as the free base). Alternatively, 60 g of the vinyl ether, 650 mL of methyl t-butyl ether (MTBE), and 18 g of 5% Pd on alumina were stirred under 40 psi hydrogen pressure at 40° for 12 H. Assay yield was 87%, with a 91:9 ratio of diastereomers. At the end of the reaction age, the catalyst was removed by filtration through Solka-Floc, then the filtrate was concentrated to 140 mL.

The first batch was treated with a warm (40° C.) solution of p-toluene sulfonic acid monohydrate (575 g, 3.03 moles) in methyl-t-butyl ether (3.2 L). The p-toluene sulfonic acid salt of [2R-[2a(R*),3a]]-2-[1-[3,5-bis(trifluoromethyl) phenyl]ethoxy]-3-(4-fluorophenyl)morpholine began to crystallize during the addition. The batch was cooled to ambient temperature and hexane (24 L) was added. The batch was aged for 2 hours, then the product was collected by filtration. The solid was washed with 4:1 hexane:methyl-t-butyl ether (2×2.5 L), then dried under nitrogen (1761 g (1655 g corrected for purity) of [2R-[2a(R*),3a]]-2-[1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl) morpholine 4-methylbenzenesulfonate (salt), 94 wt % pure, 70% yield). Alternatively, to the second solution was added a solution of 16.0 g p-TsOH monohydrate in 64 mL MTBE at 35° over a 20 min period. The tosylate salt crystallized as a thick slurry. Then 520 mL of hexanes was added over 1 h, and the slurry was stirred 2 h at ambient temperature. The slurry was filtered, washed with 2×60 mL 1:4 MTBE:hexanes, and dried by air suction to give 51.9 g of the tosylate salt (75% yield) containing 0.9% of the undesired diastereomer.

HPLC conditions: Column: Zorbax RX-C18, 25 cm×4.6 mm; Mobile phase: acetonitrile:aqueous 0.005M sodium heptane sulfonate, 0.002M potassium dihydrogen phosphate, 0.0005M disodium hydrogen phosphate (75:25, v/v); Flow rate: 1.5 mL/min; Detection: UV at 220 nm; Approximate retention times: [2R-[2a(R*),3a]]-2-[1-[3,5-bis(trifluoromethyl)phenyl]-ethoxy]-3-(4-fluorophenyl) morpholine: 4.5 minutes; N-benzyl [2R-[2a(R*),3a]]-2-[1-[3,5-bis(trifluoromethyl)phenyl]-ethoxy]-3-(4-fluorophenyl)morpholine: 25.0 minutes; (2R-cis)-2-[[1-[3.5-bis(trifluoromethyl)-phenyl]ethenyl]oxy]-3-(4-fluorophenyl)-4-(phenylmethyl)mopholine: 30.0 minutes.

HPLC conditions: Column: Zorbax RX-C18, 25 cm×4.6 mm; Mobile phase: acetonitrile:aqueous 0.005M sodium heptane sulfonate, 0.002M potassium dihydrogen phosphate, 0.0005M disodium hydrogen phosphate (60:40, v/v); Flow rate: 1.5 mL/min; Detection: UV at 220 nm; Approximate retention times: [2R-[2a(R*),3a]]-2-[1-[3,5-bis(trifluoromethyl)phenyl]-ethoxy]-3-(4-fluorophenyl) morpholine: 9.0 minutes; Diastereomer of [2R-[2a(R*),3a]]-2-[1-[3,5-bis(trifluoromethyl)phenyl]-ethoxy]-3-(4-fluorophenyl)morpholine: 11.0 minutes (epimeric at methyl group)

EXAMPLE 109

[2R-[2a(R*),3a]]-5-[[2-[1-[3,5-bis(trifluoromethyl) phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl] methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one

Powdered potassium carbonate (682 g, 4.93 moles) was added to a solution of [2R-[2a(R*),3a]]-2-[1-[3,5-bis (trifluoromethyl)phenyl]-ethoxy]-3-(4-fluorophenyl) morpholine 4-methylbenzenesulfonate (salt) (1254 g, 2.06 moles), N-methylcarboxy-2-chloroacetamidrazone (375 g, 2.26 moles), and dimethylformamide (10 L). The reaction was maintained between 15° and 25° C. and aged for 2.5 hours. The batch was diluted with 1:1 hexane:methyl-t-butyl ether (10 L) and 10.9% aqueous ammonium chloride (11 L). The phases were partitioned and the aqueous phase was back extracted with 1:1 hexane:methyl-t-butyl ether (2×8 L), followed by 1:2 hexane:methyl-t-butyl ether (8 L). The combined organic phases were washed with water (2×15 L), then vacuum concentrated. The resulting material was dissolved in xylenes (20 L) and heated to reflux (137° C.). The solution was maintained at reflux for 3 hours, then cooled to ambient temperature, whereupon [2R-[2a(R*),3a]]-5-[[2-[1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl) -4-morpholinyl]methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one crystallized. The batch was aged overnight, then filtered. The filter cake was washed with xylenes (2 L), then hexanes (2×2 L), then dried under vacuum at 30° C. for three days (696 g, 63% yield of [2R-[2a(R*),3a]]-5-[[2-[1-[3,5-bis (trifluoromethhyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one).

Alternatively, the title product may be prepared as follows from the amine TsOH salt, (1.90 Kg, 3.12 mol); N-methylcarboxyl-2-chloroacetamidrazone (516.3 g, 3.12 mol); K_2CO_3 (1.08 kg, 2.5 eq.); and DMSO (15.6 L). To a suspension of amine salt and powder K_2CO_3 in DMSO (7.8 L) at 20° C. is added a solution of N-methylcarboxyl-2-chloroacetamidrazone in DMSO (7.8 L). The first half of the solution is added quickly, (with slight cooling with ice water bath) then the remaining half is added over a period of 1 hr. After the addition, the reaction is checked by LC, and the reaction is quenched with cold water (15 L) and methyl-t-butyl ether (MTBE) (30 L) solution. The organic layr is separated, and washed with water, sat. $NaHCO_3$, brine, and water (20 L/each) respectively. The aqueous layers is back extracted with additional MTBE (15 L). The combined MTBE solution is concentrated to an oil. The resulting crude product is dissolved in xylene (25 L) and diisopropylethylamine (6.25 L) and is heated to reflux (~135° C.) and the reaction is monitored by LC. The reaction takes 4–6 hours

to complete, the the reaction solution is cooled down to room temperature overnight and filter to get the title product (expect 1.33 kg, ~80%, typically purity 98.5A %).

The resulting crude product is dissolved in hot methanol (13.3 L), added charcoal 133 g, then filtered and the charcoal is washed with hot methanol (3.3 L). The methanol solution is cooled down to room temperature, then water (7 L) is added dropwise. After being stirred at room temperature for 2 hrs, the suspension is filtered to isolate purified product as a white crystalline compound (expect 1.20 kg, 90% recovery, typical purity, 99.5A %).

HPLC conditions: Column: Zorbax RX-C8, 25 cm×4.6 mm; Mobile phase: (A) acetonitrile, (B) 0.1% aqueous phosphoric acid; Linear gradient: 40:60 A:B to 70:30 A:B in 10 minutes; Flow rate: 1.5 mL/min; Detection: UV at 220 nm; Approximate retention times: Alkylated intermediate: 5.7 minutes; [2R-[2a(R*),3a]]-5-[[2-[1-[3,5-bis (trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one: 8.2 minutes.

EXAMPLE 110

[2R-[2a(R*),3a]]-[3-[[2-[1-[3,5-bis(trifluoromethyl) phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl] methyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl] phosphonic acid compound with 1-deoxy-1-(methylamino)-D-glucitol (1:2)

A solution of sodium bis(trimethylsilyl)amide (2.25 L, 1.0M in tetrahydrofuran) was added dropwise to a cold (−0.5° C.) solution of [2R-[2a(R*),3a]]-5-[[2-[1-[3,5-bis (trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one (480.6 g, 0.9 moles) and tetrabenzyl pyrophosphate (576 g, 1.08 moles) in tetrahydrofuran (6.75 L) while maintaining the temperature at 0°–5° C. Additional tetrabenzyl pyrophosphate (48.4 g, 90 moles) was added and the resulting solution was stirred for 45 minutes. The reaction was quenched by pouring the solution into a vigorously stirred mixture of methyl-t-butyl ether (18 L) and saturated aqueous sodium bicarbonate (9 L). The organic layer was separated and sequentially washed with saturated aqueous sodium bicarbonate (2×9 L), 10% aqueous sodium hydrogen sulfate (2×9 L), saturated aqueous sodium chloride (2×9 L), and water (9 L). All aqueous layers were combined and back extracted with methyl-t-butyl ether (9 L). The methyl-t-butyl ether layers were combined and concentrated. The resulting material was dissolved in methanol (4 L), then N-methyl-D-glucamine (440 g, 2.25 moles) in pyrogen-free water (800 mL) was added. The resulting solution was subjected to hydrogenation (40 psi) with 5% palladium-on-carbon (45 g) overnight.

The batch was filtered through Solka Floc, then washed with methanol (4 L). The batch was purified by HPLC. For each injection, about 400 mL of the filtrate was diluted with water (200 mL) and methanol (50 mL), then loaded on a Waters Delta-Pak C18 column (48×300 mm) and eluted with acetonitrile:water. The rich cuts were combined and lyophilized (931 g, 87% yield of [2R-[2a(R*),3a]]-[3-[[2-[1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]phosphonic acid compound with 1-deoxy-1-(methylamino)-D-glucitol (1:2), i.e. 2-(S)-(1-(R)-(3,5-bis (trifluoro-methyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1-phosphoryl-5-oxo-4H-1,2,4-triazolo) methylmorpholine, bis(N-methyl-D-glucamine)).

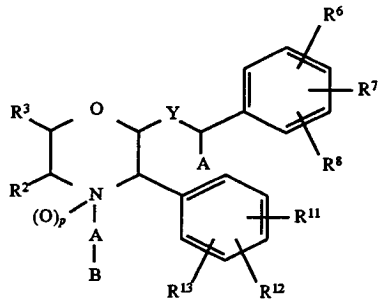
HPLC conditions: Column: Zorbax RX-C8, 25 cm×4.6 mm; Mobile phase: (A) acetonitrile, (B) 0.1% aqueous phosphoric acid; Linear gradient: 40:60 A:B to 70:30 A:B in 10 minutes, hold for 5 minutes; Flow rate: 1.5 mL/min; Detection: UV at 220 nm; Approximate retention times: [2R-[2a(R*),3a]]-[3-[[2-[1-[3,5-bis(trifluoromethyl)phenyl] ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]phosphonic acid: 4.2 minutes; Dibenzyl intermediate: 14.3 minutes.

Prep. HPLC conditions: Column: Waters Delta-Pak C18, 48×300 mm, 15 mm particle size, 100 Å pore size; Mobile phase: (A) acetonitrile, (B) water; Step gradient: 10:90 A:B for 10 min, 30:70 A:B for 13 min, 35:65 A:B for 10 min, 40:60 A:B for 10 min; Flow rate: 75 mL/min.

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications with the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compounds selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

What is claimed is:

1. A compound of structural formula:



or a pharmaceutically acceptable salt thereof, wherein:

R^2 and R^3 are independently selected from the group consisting of:

(1) hydrogen,

(2) C_{1-6} alkyl, unsubstituted or substituted with one or more of the substituents selected from:

(a) hydroxy,

(b) oxo,

(c) C_{1-6} alkoxy,

(d) phenyl-C_{1-3} alkoxy,

(e) phenyl,

(f) —CN,

(g) halo,

(h) $—NR^9R^{10}$, wherein R^9 and R^{10} are independently selected from:

(i) hydrogen,

(ii) C_{1-6} alkyl,
(iii) hydroxy-C_{1-6} alkyl, and
(iv) phenyl,
(i) $—NR^9COR^{10}$,
(j) $—NR^9CO_2R^{10}$,
(k) $—CONR^9R^{10}$,
(l) $—COR^9$, and
(m) $—CO_2R^9$,
(3) C_{2-6} alkenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
(a) hydroxy,
(b) oxo,
(c) C_{1-6} alkoxy,
(d) phenyl-C_{1-3} alkoxy,
(e) phenyl,
(f) —CN,
(g) halo,
(h) $—CONR^9R^{10}$,
(i) $—COR^9$,
(j) $—CO_2R^9$;
(4) C_{2-6} alkynyl;
(5) phenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
(a) hydroxy,
(b) C_{1-6} alkoxy,
(c) C_{1-6} alkyl,
(d) C_{2-5} alkenyl,
(e) halo,
(f) —CN,
(g) $—NO_2$,
(h) $—CF_3$,
(i) $—(CH_2)_m—NR^9R^{10}$, wherein m is 0, 1 or 2,
(j) $—NR^9COR^{10}$,
(k) $—NR^9CO_2R^{10}$,
(l) $—CONR^9R^{10}$,
(m) $—CO_2NR^9R^{10}$,
(n) $—COR^9$, and
(o) $—CO_2R^9$;
or the groups R^2 and R^3 are joined together to form a carbocyclic ring selected from the group consisting of:
(a) cyclopentyl,
(b) cyclohexyl,
(c) phenyl,
and wherein the carbocyclic ring is unsubstituted or substituted with one or more substituents selected from:
(i) C_{1-6}alkyl,
(ii) C_{1-6}alkoxy,
(iii) $—NR^9R^{10}$,
(iv) halo, and
v) trifluoromethyl;
or the groups R^2 and R^3 are joined together to form a heterocyclic ring selected from the group consisting of:
(a) pyrrolidinyl,
(b) piperidinyl,
(c) pyrrolyl,
(d) pyridinyl,
(e) imidazolyl,
(f) furanyl,
(g) oxazolyl,
(h) thienyl, and
(i) thiazolyl,
and wherein the heterocyclic ring is unsubstituted or substituted with one or more substituent(s) selected from:
(i) C_{1-6}alkyl,
(ii) oxo,
(iii) C_{1-6}alkoxy,
(iv) $—NR^9R^{10}$,
(v) halo, and
(vi) trifluoromethyl;
R^6, R^7 and R^8 are independently selected from the group consisting of:
(1) hydrogen;
(2) C_{1-6} alkyl, unsubstituted or substituted with one or more of the substituents selected from:
(a) hydroxy,
(b) oxo,
(c) C_{1-6} alkoxy,
(d) phenyl-C_{1-3} alkoxy,
(e) phenyl,
(f) —CN,
(g) halo,
(h) $—NR^9R^{10}$,
(i) $—NR^9COR^{10}$,
(j) $—NR^9CO_2R^{10}$,
(k) $—CONR^9R^{10}$,
(l) $—COR^9$, and
(m) $—CO_2R^9$;
(3) C_{2-6} alkenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
(a) hydroxy,
(b) oxo,
(c) C_{1-6} alkoxy,
(d) phenyl-C_{1-3} alkoxy,
(e) phenyl,
(f) —CN,
(g) halo,
(h) $—CONR^9R^{10}$,
(i) $—COR^9$, and
(j) $—CO_2R^9$;
(4) C_{2-6} alkynyl;
(5) phenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
(a) hydroxy,
(b) C_{1-6} alkoxy,
(c) C_{1-6} alkyl,
(d) C_{2-5} alkenyl,
(e) halo,
(f) —CN,
(g) $—NO_2$,
(h) $—CF_3$,
(i) $—(CH_2)_m—NR^9R^{10}$,
(j) $—NR^9COR^{10}$,
(k) $—NR^9CO_2R^{10}$,
(l) $—CONR^9R^{10}$,
(m) $—CO_2NR^9R^{10}$,
(n) $—COR^9$, and
(o) $—CO_2R^9$;
(6) halo,
(7) —CN,
(8) $—CF_3$,
(9) $—NO_2$,
(10) $—SR^{14}$, wherein R^{14} is hydrogen or C_{1-5}alkyl,
(11) $—SOR^{14}$,
(12) $—SO_2R^{14}$,
(13) NR^9COR^{10},
(14) $CONR^9COR^{10}$,
(15) NR^9R^{10},
(16) $NR^9CO_2R^{10}$,
(17) hydroxy,
(18) C_{1-6}alkoxy,
(19) COR^9,
(20) CO_2R^9,
(21) 2-pyridyl,
(22) 3-pyridyl,

(23) 4-pyridyl,
(24) 5-tetrazolyl,
(25) 2-oxazolyl, and
(26) 2-thiazolyl;

R^{11}, R^{12} and R^{13} are independently selected from the definitions of R^6, R^7 and R^8, or —OX;

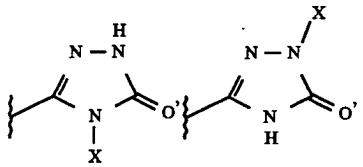
A is selected from the group consisting of:

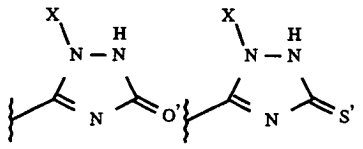
(1) C_{1-6} alkyl, unsubstituted or substituted with one or more of the substituents selected from:
(a) hydroxy,
(b) oxo,
(c) C_{1-6} alkoxy,
(d) phenyl-C_{1-3} alkoxy,
(e) phenyl,
(f) —CN,
(g) halo, wherein halo is fluoro, chloro, bromo or iodo,
(h) —NR^9R^{10},
(i) —NR^9COR^{10},
(j) —$NR^9CO_2R^{10}$,
(k) —$CONR^9R^{10}$,
(l) —COR^9, and
(m) —CO_2R^9;

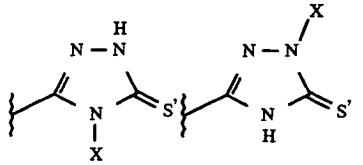
(2) C_{2-6} alkenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
(a) hydroxy,
(b) oxo,
(c) C_{1-6} alkoxy,
(d) phenyl-C_{1-3} alkoxy,
(e) phenyl,
(f) —CN,
(g) halo,
(h) —$CONR^9R^{10}$,
(i) —COR^9, and
(j) —CO_2R^9; and

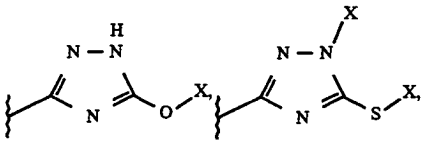
(3) C_{2-6} alkynyl;

B is a heterocycle, wherein the heterocycle is selected from the group consisting of:









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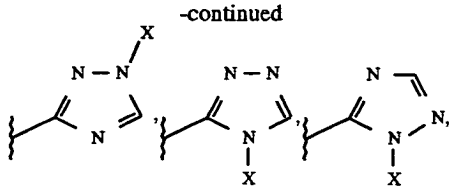
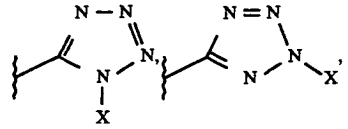
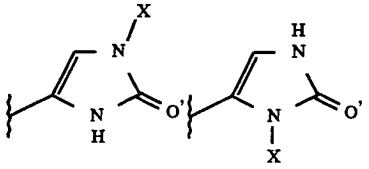
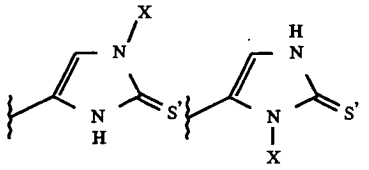
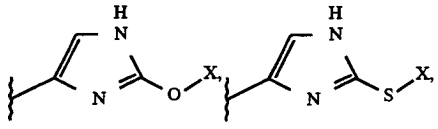
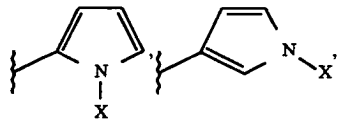


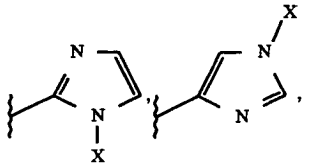


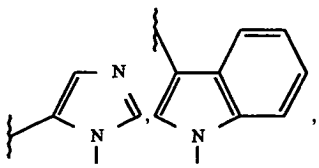


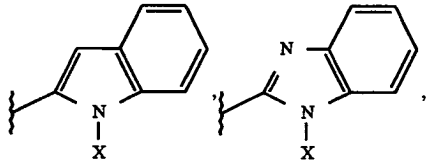












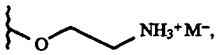
and wherein the heterocycle is substituted in addition to —X with one or more substituent(s) selected from:
(i) hydrogen;
(ii) C_{1-6} alkyl, unsubstituted or substituted with halo, —CF_3, —OCH_3, or phenyl,
(iii) C_{1-6} alkoxy,
(iv) oxo,
(v) hydroxy,

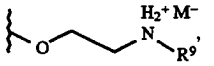
(vi) thioxo,
(vii) —SR^9,
(viii) halo,
(ix) cyano,
(x) phenyl,
(xi) trifluoromethyl,
(xii) —$(CH_2)_m$—NR^9R^{10},
(xiii) —NR^9COR^{10},
(xiv) —$CONR^9R^{10}$,
(xv) —CO_2R^9, and
(xvi) —$(CH_2)_m$—OR^9;

p is 0 or 1;

X is selected from:

(a) —$PO(OH)O^-{\bullet}M^+$, wherein M^+ is a pharmaceutically acceptable monovalent counterion,
(b) —$PO(O^-)_2{\bullet}2M^+$,
(c) —$PO(O^-)_2{\bullet}D^{2+}$, wherein D^{2+} is a pharmaceutically acceptable divalent counterion,
(d) —$CH(R^4)$—$PO(OH)O^-{\bullet}M^+$, wherein R^4 is hydrogen or C_{1-3} alkyl,
(e) —$CH(R^4)$—$PO(O^-)_2{\bullet}2M^+$,
(f) —$CH(R^4)$—$PO(O^-)_2{\bullet}D^{2+}$,
(g) —$SO_3^-{\bullet}M+$,
(h) —$CH(R^4)$—$SO_3^-{\bullet}M^+$,
(i) —CO—CH_2CH_2—$CO_2^-{\bullet}M^+$,
(j) —$CH(CH_3)$—O—CO—R^5, wherein R^5 is selected from the group consisting of:


(i)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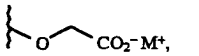
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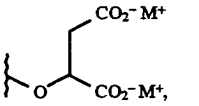
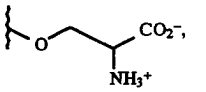
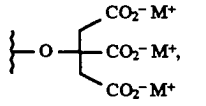
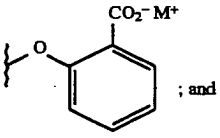

(iv)


(v)


(vi)


(vii)

; and

(k) hydrogen, with the proviso that if p is 0 and none of R^{11}, R^{12} or R^{13} are —OX, then X is other than hydrogen;

Y is selected from the group consisting of:

(1) a single bond,
(2) —O—,
(3) —S—,
(4) —CO—,
(5) —CH_2—,
(6) —CHR^{15}—, and
(7) —$CR^{15}R^{16}$—, wherein R^{15} and R^{16} are independently selected from the group consisting of:

(a) C_{1-6} alkyl, unsubstituted or substituted with one or more of the substituents selected from:
(i) hydroxy,
(ii) oxo,
(iii) C_{1-6} alkoxy,
(iv) phenyl-C_{1-3} alkoxy,
(v) phenyl,
(vi) —CN,
(vii) halo,
(viii) —NR^9R^{10},
(ix) —NR^9COR^{10},
(x) —$NR^9CO_2R^{10}$,
(xi) —$CONR^9R^{10}$,
(xii) —COR^9, and
(xiii) —CO_2R^9;

(b) phenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
(i) hydroxy,
(ii) C_{1-6} alkoxy,
(iii) C_{1-6} alkyl,
(iv) C_{2-5} alkenyl,
(v) halo,
(vi) —CN,
(vii) —NO_2,
(viii) —CF_3,
(ix) —$(CH_2)_m$—NR^9R^{10},
(x) —NR^9COR^{10},
(xi) —$NR^9CO_2R^{10}$,
(xii) —$CONR^9R^{10}$,
(xiii) —$CO_2NR^9R^{10}$,
(xiv) —COR^9, and
(xv) —CO_2R^9;

Z is selected from:

(1) hydrogen,
(2) C_{1-6} alkyl, and
(3) hydroxy, with the proviso that if Y is —O—, then Z is other than hydroxy, and with the further proviso that if Y is —CHR^{15}—, then Z and R^{15} may be joined together to form a double bond between the two carbon atoms.

2. The compound of claim 1 wherein:

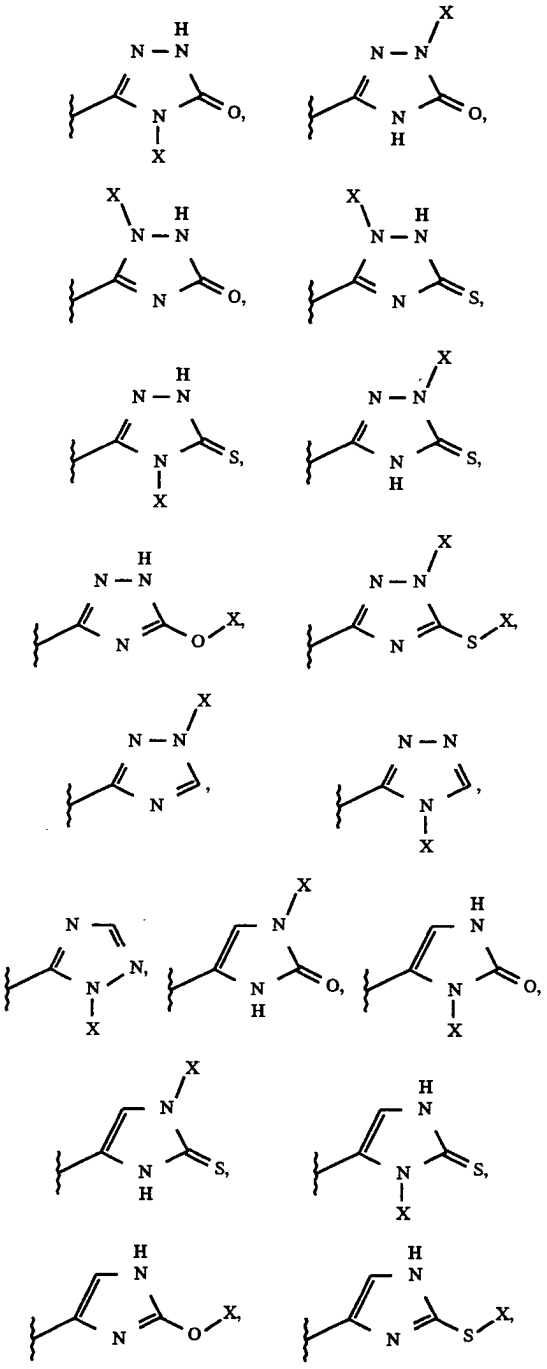
R^2 and R^3 are independently selected from the group consisting of:
(1) hydrogen,
(2) C_{1-6} alkyl,
(3) C_{2-6} alkenyl, and
(4) phenyl;

R^6, R^7 and R^8 are independently selected from the group consisting of:
(1) hydrogen,
(2) C_{1-6} alkyl,
(3) fluoro,
(4) chloro,
(5) bromo,
(6) iodo, and
(7) —CF_3;

R^{11}, R^{12} and R^{13} are independently selected from the group consisting of:
(1) fluoro,
(2) chloro,
(3) bromo, and
(4) iodo;

A is unsubstituted C_{1-6} alkyl;

B is selected from the group consisting of:



p is 0;

X is selected from:

(a) —PO(OH)O$^-$•M$^+$, wherein M$^+$ is a pharmaceutically acceptable monovalent counterion,

(b) —PO(O$^-$)$_2$•2M$^+$,

(c) —PO(O$^-$)$_2$•D^{2+}, wherein D^{2+} is a pharmaceutically acceptable divalent counterion,

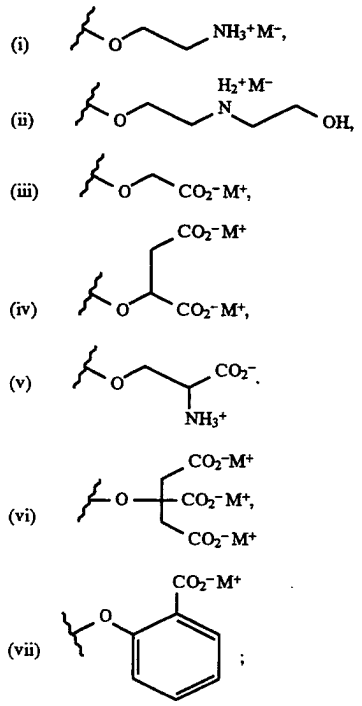
(d) —CH(R^4)—PO(OH)O$^-$•M$^+$, wherein R^4 is hydrogen or methyl,

(e) —CH(R^4)—PO(O$^-$)$_2$•2M$^+$,

(f) —CH(R^4)—PO(O$^-$)$_2$•D^{2+},

(g) —CO—CH$_2$CH$_2$—CO$_2^-$•M$^+$,

(h) —CH(CH$_3$)—O—CO—R^5, wherein R^5 is selected from the group consisting of:



and

Y is —O—;

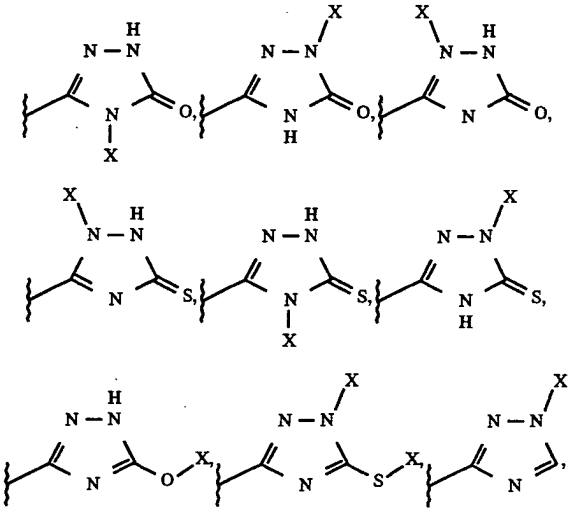
Z is hydrogen or C$_{1-4}$ alkyl.

3. The compound of claim 1 wherein Z is C$_{1-4}$ alkyl.

4. the compound of claim 1 wherein Z is —CH$_3$.

5. The compound of claim 1 wherein A is —CH$_2$— or —CH(CH$_3$)—.

6. The compound of claim 1 wherein —B is selected from the group consisting of:



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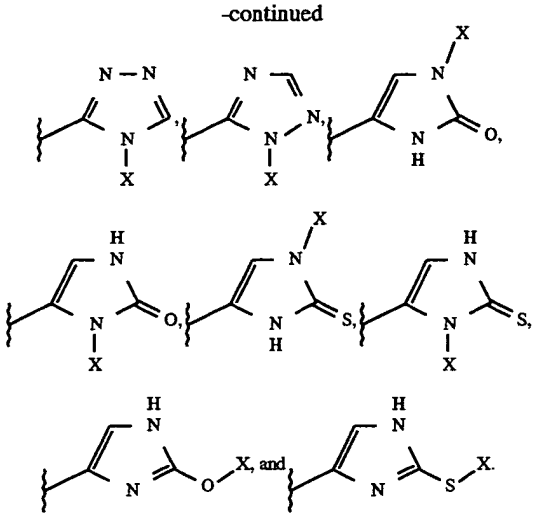
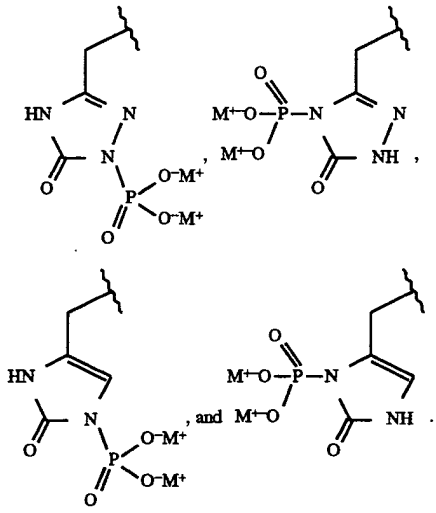


7. The compound of claim 1 wherein —A—B is selected from the group consisting of:

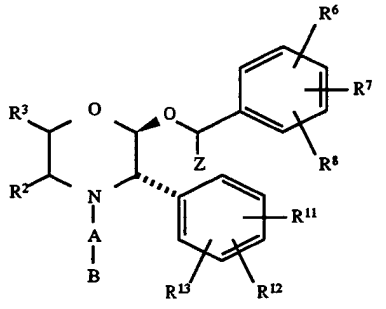


8. The compound of claim 1 wherein X is selected from the group consisting of:

(a) —$PO(O^-)_2 \cdot 2M^+$, wherein M^+ is a pharmaceutically acceptable monovalent counterion, and

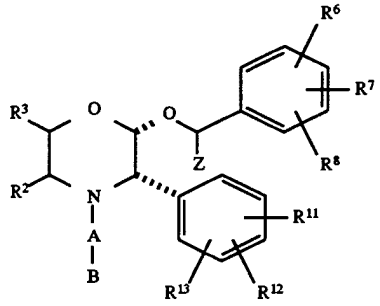
(b) —$PO(O^-)_2 \cdot D^{2+}$, wherein D^{2+} is a pharmaceutically acceptable divalent counterion.

9. The compound of claim 1 of the structural formula II:



or a pharmaceutically acceptable salt thereof.

10. The compound of claim 1 of the structural formula III:



or a pharmaceutically acceptable salt thereof.

11. A compound which is selected from the group consisting of:

(1) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine N-oxide;

(2) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(4-monophosphoryl-5-oxo-1H-1,2,4-triazolo)methyl)morpholine;

(3) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(1-monophosphoryl-5-oxo-1H-1,2,4-triazolo)methyl)morpholine;

(4) 2-(R)-1(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(2-monophosphoryl-5-oxo-1H-1,2,4-triazolo)methyl)morpholine;

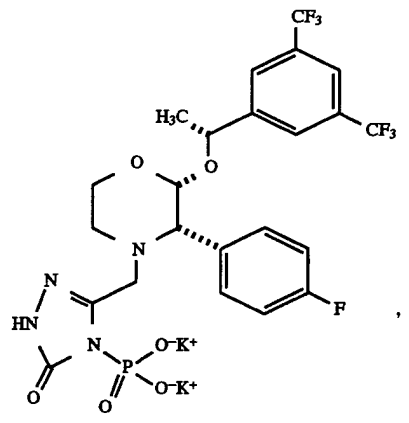
(5) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-4-fluoro)-phenyl-4-(3-(5-oxyphosphoryl-1H-1,2,4-triazolo)methyl)morpholine;

(6) 2-(S)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(1-phosphoryl-5-oxo-4H-1,2,4-triazolo)methyl)morpholine;

or a pharmaceutically acceptable salt thereof.

12. The compound of claim 11 wherein the pharmaceutically acceptable salt is the bis(N-methyl-D-glucamine) salt.

13. A compound which is selected from the group consisting of:



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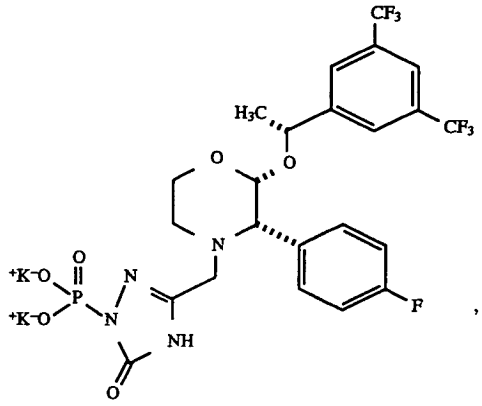

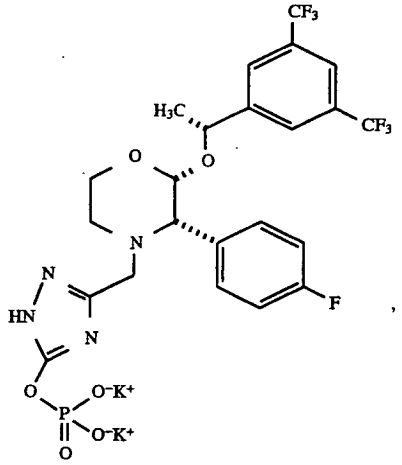

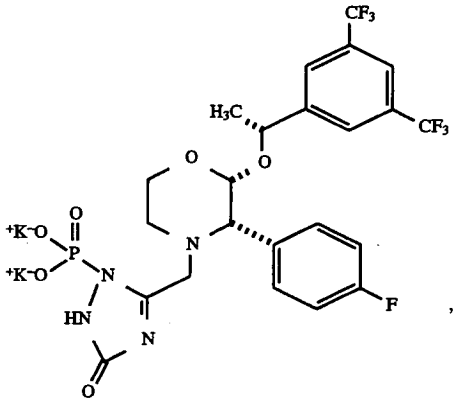

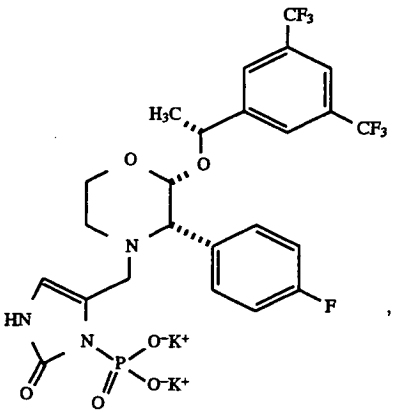

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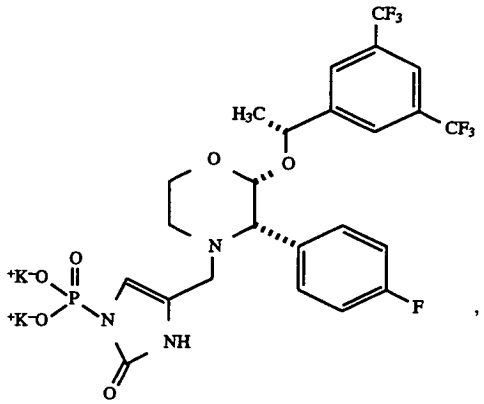
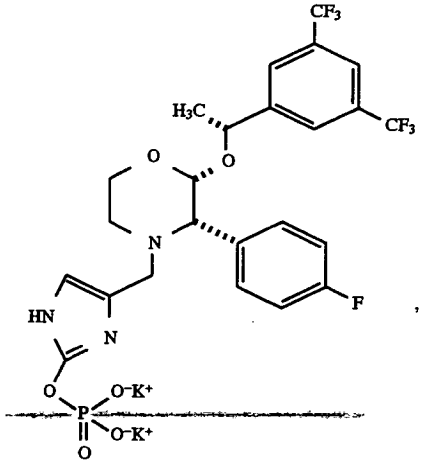




wherein K^+ is a pharmaceutically acceptable counterion.

14. A compound which is:

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1-phosphoryl-5-oxo-4H-1,2,4-triazolo)methylmorpholine;

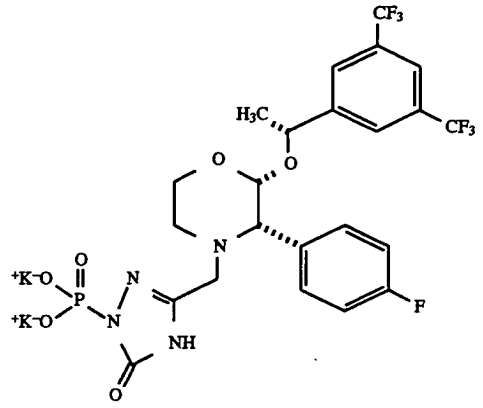
or a pharmaceutically acceptable salt thereof.

15. The compound of claim **14** wherein the pharmaceutically acceptable salt is the bis(N-methyl-D-glucamine) salt.

16. A compound which is

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1-phosphoryl-5-oxo-4H-1,2,4-triazolo)methylmorpholine, bis(N-methyl-D-glucamine).

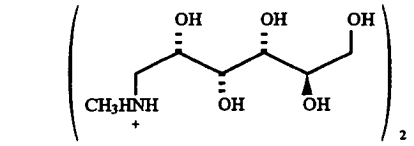
17. A compound which is:

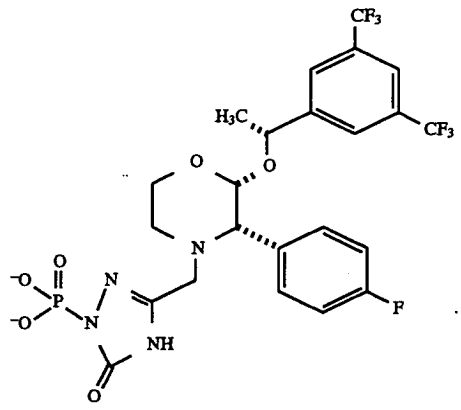


wherein K^+ is a pharmaceutically acceptable counterion.

18. The compound of claim 17 wherein K^+ is N-methyl-D-glucamine.

19. A compound which is:



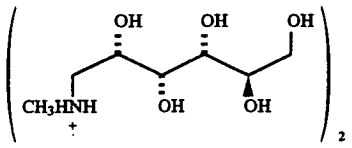


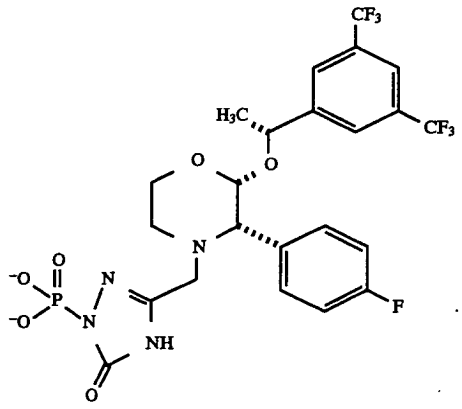
20. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of the compound of claim 1.

21. The pharmaceutical composition of claim 20 wherein the pharmaceutically acceptable carrier comprises water.

22. The pharmaceutical composition of claim 20 wherein the pharmaceutically acceptable carrier comprises a physiologically acceptable saline solution.

23. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a compound which is:





24. A method for antagonizing the effect of substance P at its receptor site or for the blockade of neurokinin-1 receptors in a mammal which comprises the administration to the mammal of the compound of claim 1 in an amount that is effective for antagonizing the effect of substance P at its receptor site or for the blockade of neurokinin-1 receptors in the mammal.

25. A method of treating or preventing pain or nociception which comprises the administration to the mammal of an effective amount of the compound of claim 1.

* * * * *

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants :	Conrad P. Dorn et al.	
Patent No. :	5,691,336	Case No.: 19189IA
Issued :	November 25, 1997	
Application No. :	08/525,870	
Filed :	September 8, 1995	
For :	MORPHOLINE COMPOUNDS ARE PRODRUGS USEFUL AS TACHYKININ RECEPTOR ANTAGONISTS	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION

Sir:

Transmitted herewith is a Certificate of Correction for the above captioned issued patent. Applicants respectfully request entry of the Certificate of Correction to correct the error in the structure as printed in the Abstract and the error in the structure as printed in Claim 1.

This mistake is clearly disclosed in the records of the Office. Attached hereto is a copy of the Abstract in the application as filed on September 8, 1995, and a copy of Claim 31 (renumbered as Claim 1 in the patent) in the Amendment of October 18, 1995, which show that the structure in the Abstract and the structure in Claim 1 should have been printed with a "Z" at the position adjacent to "Y" (rather then an "A" as printed in the patent).

This correction was not due to Applicants mistake so no fee is believed due. Any additional fees required in connection with this request may be taken from Merck Deposit Account No. 13-2755.

EXPRESS MAIL CERTIFICATE
DATE OF DEPOSIT 3-20-08
EXPRESS MAIL NO. EV422536057US
I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS EXPRESS MAIL "POST OFFICE TO ADDRESSEE" ON THE ABOVE DATE IN AN ENVELOPE ADDRESSED TO COMMISSIONER FOR PATENTS, P.O. BOX 1450, ALEXANDRIA, VIRGINIA 22313-1450.
MAILED BY Kathy Kowalski
DATE 3/20/08

Respectfully submitted,

By _____
J. Eric Thies
Reg. No. 35,382
Attorney for Applicant
MERCK & CO., Inc.
P.O. Box 2000
Rahway, New Jersey 07065-0907
(732) 594-3904

Date: March 20, 2008

Substitute for PTO/SB/44 (07-07) "Certificate of Correction"
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO: 5,691,336

APPLICATION NO.: 08/525,870

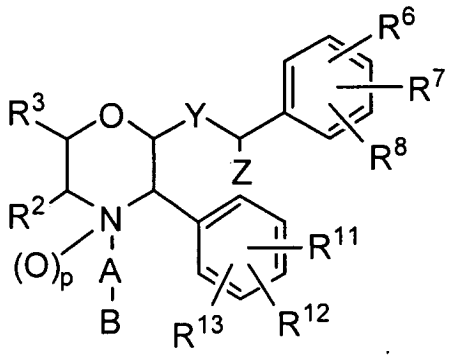
ISSUE DATE: November 25, 1997

INVENTOR(S): Conrad P. Dorn et al.

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

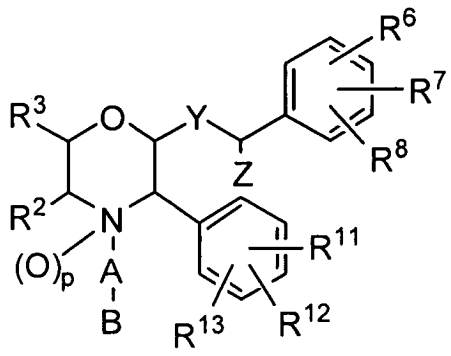
Abstract

Item [57], ABSTRACT, replace the structure with the following structure:



Claims

In Claim 1, column 146, lines 38-51, replace the structure with the following structure:



MAILING ADDRESS OF SENDER:
Merck & Co., Inc.
Patent Dept., RY60-30
P.O. BOX 2000
Rahway, NJ 07065-0907

PATENT NO. 5,691,336

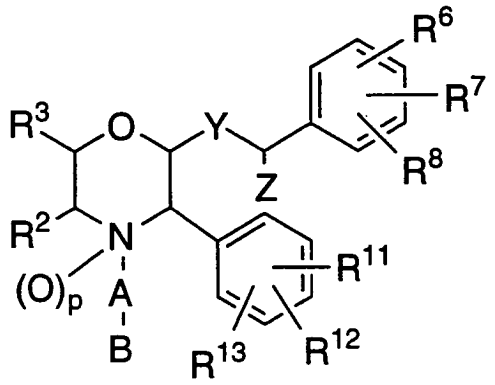
No. of additional copies

TITLE OF THE OF INVENTION

MORPHOLINE COMPOUNDS ARE USEFUL AS TACHYKININ RECEPTOR ANTAGONISTS

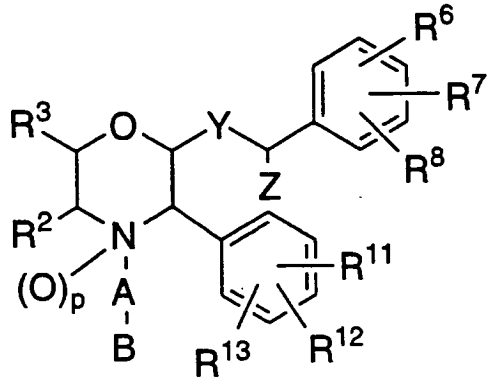
ABSTRACT OF THE INVENTION

Substituted heterocycles of the general structural formula:



are tachykinin receptor antagonists useful in the treatment of inflammatory diseases, pain or migraine, asthma, and emesis.

31. A compound of structural formula:



or a pharmaceutically acceptable salt thereof, wherein:

R^2 and R^3 are independently selected from the group consisting of:

(1) hydrogen,

(2) C_{1-6} alkyl, unsubstituted or substituted with one or more of the substituents selected from:

(a) hydroxy,

(b) oxo,

(c) C_{1-6} alkoxy,

(d) phenyl-C_{1-3} alkoxy,

(e) phenyl,

(f) -CN,

(g) halo,

(h) $-NR^9R^{10}$, wherein R^9 and R^{10} are independently selected from:

(i) hydrogen,

(ii) C_{1-6} alkyl,

(iii) hydroxy-C_{1-6} alkyl, and

(iv) phenyl,

(i) $-NR^9COR^{10}$,

(j) $-NR^9CO_2R^{10}$,

(k) $-CONR^9R^{10}$,

EXHIBIT F

U.S. Patent No. 5,691,336
Maintenance Fee Statements

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

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J ERIC THIES
PATENT DEPARTMENT
MERCK & COMPANY INC
P O BOX 2000

MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,691,336	**$850.00**	**$0.00**	**04/19/01**	**08/525,870**	**11/25/97**	**09/08/95**	**04**	**NO**	**19189IA**

UNITED STATES PATENT AND TRADEMARK OFFICE

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J ERIC THIES
PATENT DEPARTMENT
MERCK & COMPANY INC
P O BOX 2000

MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,691,336	**$2,300.00**	**$0.00**	**03/29/05**	**08/525,870**	**11/25/97**	**09/08/95**	**08**	**NO**	**191891A**

EXHIBIT G

EMEND for Injection
Chronology of Major Communications with the FDA

BRIEF DESCRIPTION OF REPRESENTATIVE SIGNIFICANT ACTIVITIES DURING THE REGULATORY PERIOD FOR FOSAPREPITANT

Reg Number	Compound ID	Filing Date	Serial Number	Activity	Description
48,924	0517	9/28/1995	"0000"	Initial Filing	L-000758298 Initial IND
48,924	0517	10/25/1995	"0001"	Information Amendment - Chemistry/Microbiology (CMC)	Submitting room temperature stability data for Injection after reconstitution in 0.9% sodium chloride solution. L-758,298 was reconstituted to three concentrations, .004 mg/ml, .1 mg/ml, .4 mg/ml which spans the concentration range proposed for clinical studies
48,924	0517	11/1/1995	"0002"	Information Amendment - Chemistry/Microbiology (CMC)	Composition, method of manufacture and control and sample label copy for Placebo L-758,298 for Injection, 6 mg/vial and 50 mg/vial.
48,924	0517	12/8/1995	"0003"	Protocol Amendment - Change in Protocol	Protocol/Amendment No.: 001-00/Single Center
48,924	0517	1/18/1996	"0004"	Protocol Amendment - Change in Protocol	Protocol/Amendment No.: 001-02.
48,924	0517	2/8/1996	"0005"	Information Amendment - Chemistry/Microbiology (CMC)	Injection ZOFRAN 2mg/mL
48,924	0517	3/1/1996	"0006"	Protocol Amendment - New Protocol	A Two-part, Placebo-Controlled, In-Clinic Study to Explore the Preliminary Safety, Tolerability, and Efficacy of Intravenous of L-758,298 in the Acute Treatment of Migraine/Protocol No. 003
48,924	0517	3/8/1996	"0007"	Information Amendment - Chemistry/Microbiology (CMC)	Compostiion and method of manufacture and control for Substance P sourced from CLINALFA AG, Switzerland.
48,924	0517	3/8/1996	"0008"	Protocol Amendment - New Protocol	Protocol/Amendment No.: 005-00
48,924	0517	3/8/1996	"0009"	Protocol Amendment - New Protocol	Protocol/Amendment No.: 004-00
48,924	0517	3/13/1996	"0010"	Protocol Amendment - Change in Protocol	Protocol/Amendment No.: 001-03. Represents a Change to Protocol Numbers 001-00, 001-01, and 001-02
48,924	0517	3/22/1996	"0011"	Protocol Amendment - Change in Protocol	Protocol/Amendment No.: 004-01. Represents a Change to Protocol Number 004-00
48,924	0517	3/22/1996	"0012"	Protocol Amendment - Change in Protocol	Protocol/Amendment No.: 005-01. Represents a Change to Protocol Number 005-00
50,283	0869	4/9/1996	"0000"	Initial Filing	Original IND
50,283	0869	4/16/1996	"0001"	General Correspondence	submit referenced omitted from original IND
50,283	0869	4/19/1996		Incoming Agency Correspondence	FDA ack letter of original IND
48,924	0517	4/25/1996	"0014"	Protocol Amendment - Change in Protocol	Protocol/Amendment No.: 001-04. Represents a Change to Protocol Numbers 001-00, 001-01, 001-02, and 001-03
48,924	0517	5/1/1996	"0015"	General Correspondence	Comments regarding Protocol 001
48,924	0517	5/16/1996	"0016"	Protocol Amendment - Change in Protocol	This amendment provides for a change in the dosing regimen based on clinical data showing this regimen to be safe and well tolerated in healthy male volunteers. Age range has been expanded to 18-55 years old.
48,924	0517	5/20/1996	"0017"	Protocol Amendment - Change in Protocol	This amendment provides for revisions to the Patient Exclusion Criteria. Patients taking calcium blockers, and patients with a Karpofsky score of <60 have been added to the exclusion criteria listing
50,283	0869	5/21/1996	"0002"	Information Amendment - Chemistry/Microbiology (CMC)	Information Amendment - Chemistry, Manufacturing and Control
48,924	0517	6/4/1996	"0018"	Protocol Amendment - Change in Protocol	This amendment provides for revisions to the Background and Rationale, Safety Measurements and Inclusion Criteria sections to allow for inclusion of women of childbearing potential in the study.
50,283	0869	6/6/1996		Incoming Agency Correspondence	FDA recommend of eval of liver and thyroid function in future clin studies
50,283	0869	6/13/1996	"0003"	Protocol Amendment - Change in Protocol	Protocol Amendment - Change in Protocol (Protocol No. 002)
48,924	0517	6/26/1996	"0019"	Protocol Amendment - Change in Protocol	Protocol/Amendment No.: 004-03. Represents a Change to Protocol Numbers 004-00, 004-01, and 004-02

BRIEF DESCRIPTION OF REPRESENTATIVE SIGNIFICANT ACTIVITIES DURING THE REGULATORY PERIOD FOR FOSAPREPITANT

Reg Number	Compound ID	Filing Date	Serial Number	Activity	Description
50,283	0869	7/16/1996	"0004"	Protocol Amendment - New Protocol	Protocol Amendment - New Protocol (003)
50,283	0869	8/15/1996		Incoming Agency Correspondence	CMC comments on original IND
50,283	0869	8/29/1996	"0005"	Information Amendment - Pharmacology/Toxicology	Information Amendment - Pharmacology/Toxicology
50,283	0869	9/6/1996	"0006"	Protocol Amendment - Change in Protocol	Protocol Amendment - Change in Protocol (003)
50,283	0869	9/12/1996	"0008"	Information Amendment - Chemistry/Microbiology (CMC)	Information Amendment - Chemistry, Manufacturing and Control
50,283	0869	9/12/1996	"0007"	Protocol Amendment - New Protocol	Protocol Amendment - New Protocol (004)
48,924	0517	10/10/1996	"0021"	Protocol Amendment - Change in Protocol	Addtional U.S. Clinical Monitor; Replacement Primary Investigator; Development & Reproductive Toxicity Summaries Added; Various Changes to the Study Design; Appendices 4-6 were Updated
50,283	0869	10/10/1996	"0009"	Protocol Amendment - Change in Protocol	Protocol Amendment - Change in Protocol (004)
50,283	0869	11/11/1996	"0010"	Protocol Amendment - New Protocol	Protocol Amendment - New Protocol (Protocol No. 005)
50,283	0869	11/14/1996	"0011"	Information Amendment - Chemistry/Microbiology (CMC)	Information Amendment - Chemistry, Manufacturing and Control
48,924	0517	11/19/1996	"0023"	Protocol Amendment - Change in Protocol	Rick Reinhardt, M.D. added as a Clinical Monitor. Also, this amendment provides for revisions to the Clinical Experience section, the inclusion of a 100mg dose, revisions to the infusion procedures, and the standardization of rescue medication.
48,924	0517	11/22/1996	"0024"	Information Amendment - Chemistry/Microbiology (CMC)	Update stability data for L-758,298 drug substance
50,283	0869	12/2/1996	"0012"	Protocol Amendment - New Protocol	Protocol Amendment - New Protocol (006)
50,283	0869	12/4/1996	"0013"	Protocol Amendment - New Protocol	Protocol Amendment - New Protocol (007)
48,924	0517	12/12/1996	"0025"	Annual Report	Annual Report 9/28/95 through 9/27/96
50,283	0869	1/6/1997	"0014"	Information Amendment - Chemistry/Microbiology (CMC)	Information Amendment - Chemistry, Manufacturing and Control
50,283	0869	1/10/1997	"0015"	Protocol Amendment - Change in Protocol	Protocol Amendment - Change in Protocol (007)
50,283	0869	1/15/1997	"0017"	Information Amendment - Chemistry/Microbiology (CMC)	Information Amendment - Chemistry, Manufacturing and Control
50,283	0869	1/15/1997	"0016"	Protocol Amendment - Change in Protocol	Protocol Amendment - Change in Protocol (002)
50,283	0869	1/21/1997	"0018"	Protocol Amendment - New Protocol	Protocol Amendment - New Protocol (008)
50,283	0869	1/27/1997	"0019"	Protocol Amendment - New Protocol	Protocol Amendment - New Protocol (009)
48,924	0517	3/6/1997	"0026"	Protocol Amendment - Change in Protocol	This amendment provides for revisions to the Clinical Design, Pharmacokinetics Measurements, and Clinical Supplies sections to adjust the dose infusion rate to better ensure accurate delivery of the actual dose delivered.
50,283	0869	3/10/1997	"0021"	Protocol Amendment - New Protocol	Protocol Amendment - New Protocol (010)
50,283	0869	4/8/1997	"0023"	Information Amendment - Chemistry/Microbiology (CMC)	Information Amendment - Chemistry, Manufacturing, and Control
50,283	0869	4/14/1997	"0025"	Protocol Amendment - New Protocol	Protocol Amendment - New Protocol (011)
50,283	0869	5/7/1997	"0026"	Information Amendment - Pharmacology/Toxicology	Information Amendment - Pharmacology/Toxicology
50,283	0869	5/19/1997	"0027"	Information Amendment - Pharmacology/Toxicology	Additional pharm/tox studies as requested
48,924	0517	5/22/1997	"0030"	Information Amendment - Chemistry/Microbiology (CMC)	Injection DECADRON phosphate, 4 mg/mL
48,924	0517	5/22/1997	"0029"	Protocol Amendment - New Protocol	In this study, the efficacy of L-758,298 in combination with dexamethasone in preventing acute and delayed chemotherapy-induced emesis will be examined in cancer patients undergoing chemotherapy prescribed for their underlying malignancy.
48,924	0517	5/23/1997	"0028"	Information Amendment - Pharmacology/Toxicology	Nonclinical Pharmacology & Toxicology Documentation
50,283	0869	6/13/1997	"0028"	Annual Report	Annual IND Progress Report

BRIEF DESCRIPTION OF REPRESENTATIVE SIGNIFICANT ACTIVITIES DURING THE REGULATORY PERIOD FOR FOSAPREPITANT

Reg Number	Compound ID	Filing Date	Serial Number	Activity	Description
50,283	0869	6/20/1997	"0029"	Information Amendment - Chemistry/Microbiology (CMC)	Information Amendment - C&M
50,283	0869	7/2/1997	"0030"	General Correspondence	Correction in CMC submitted 6-20-97
50,283	0869	7/7/1997	"0031"	Protocol Amendment - New Protocol	Protocol Amendment - New Protocol (013-01)
50,283	0869	7/9/1997		Incoming Agency Correspondence	Comments on pharm/tox data (SN 001 and 005)
48,924	0517	8/1/1997	"0031"	Protocol Amendment - Change in Protocol	This amendment provides for changes in the storage conditions of plasma samples for drug assay, and the inclusions of an additional allocation schedule to preserve study stratifications for gender and type of chemotherapy
50,283	0869	8/7/1997	"0034"	Response to FDA Request for Information	Response to pharm/tox questions rec'd 7-9-97
48,924	0517	8/21/1997	"0033"	Information Amendment - Chemistry/Microbiology (CMC)	C L-758,298 for Injection, 1 mg/mL
50,283	0869	8/26/1997	"0032"	Information Amendment - Pharmacology/Toxicology	Information Amendment - Pharmacology/Toxicology
48,924	0517	9/4/1997	"0034"	Information Amendment - Pharmacology/Toxicology	Nonclinical Pharmacology & Toxicology Documentation
50,283	0869	9/16/1997		Incoming Agency Correspondence	Commments on pharm/tox data (SN 026 and 027)
50,283	0869	9/16/1997	"0038"	Information Amendment - Clinical	Information Amendment - Clinical (011-01)
50,283	0869	9/19/1997	"0041"	Information Amendment - Chemistry/Microbiology (CMC)	Information Amendment - Chemistry & Manufacturing
50,283	0869	9/19/1997	"0043"	Information Amendment - Chemistry/Microbiology (CMC)	Information Amendment - Chemistry, Manufacturing & Control
50,283	0869	9/19/1997	"0039"	Protocol Amendment - Change in Protocol	Change in Protocol (013-02)
50,283	0869	9/19/1997	"0042"	Protocol Amendment - New Protocol	Protocol Amendment - New Protocol (016)
50,283	0869	9/19/1997	"0040"	Protocol Amendment - New Protocol	Protocol Amendment - New Protocol (015)
50,283	0869	10/6/1997	"0044"	Protocol Amendment - Change in Protocol	Change in Protocol (010-01)
50,283	0869	10/10/1997	"0045"	Protocol Amendment - Change in Protocol	Change in Protocol (010-02)
50,283	0869	10/13/1997	"0046"	Protocol Amendment - Change in Protocol	Protocol Amendment - Change in Protocol (Protocol No. 007)
50,283	0869	10/17/1997	"0047"	Protocol Amendment - Change in Protocol	Protocol Amendment - Change in Protocol (Protocol No. 010-03)
48,924	0517	10/24/1997	"0038"	Information Amendment - Pharmacology/Toxicology	Nonclinical Pharmacology and Toxicology Documentation
50,283	0869	11/6/1997	"0048"	Protocol Amendment - Change in Protocol	Protocol Amendment - Change in Protocol (Protocol No. 015-10)
50,283	0869	11/7/1997	"0051"	Information Amendment - Chemistry/Microbiology (CMC)	Information Amendment - Chemistry & Manufacturing Controls
50,283	0869	11/7/1997	"0050"	Protocol Amendment - Change in Protocol	Protocol Amendment - Change in Protocol (Protocol No. 006-01)
50,283	0869	11/19/1997	"0053"	Information Amendment - Chemistry/Microbiology (CMC)	Information Amendment- Chemistry and Manufacturing Controls
50,283	0869	11/20/1997	"0054"	Protocol Amendment - New Protocol	Protocol Amendment - New Protocol (Protocol No. 019)
48,924	0517	12/4/1997	"0042"	Information Amendment - Chemistry/Microbiology (CMC)	L-758,298 for injection- Polysorbate-80 based, lyophilized formulaitons Diluent for reconstitution of L-758,298, sodium citrate based.
48,924	0517	12/4/1997	"0041"	Protocol Amendment - New Protocol	The current IV formulation of L-758,298 is unstable at room temperature and requires storage conditions of -20 deg. C
48,924	0517	12/12/1997	"0045"	Annual Report	Annual IND Report 9/29/96-9/28/97
48,924	0517	12/12/1997	"0043"	Information Amendment - Chemistry/Microbiology (CMC)	Update drug substance section
48,924	0517	12/12/1997	"0044"	Protocol Amendment - Change in Protocol	This amendment provides for revisions to the Study Design and Clinical Supplies sections.
50,283	0869	12/12/1997	"0056"	Protocol Amendment - Change in Protocol	Protocol Amendment - Change in Protocol (Protocol No. 007-02)
50,283	0869	12/18/1997	"0058"	General Correspondence	Resp to req for add'l on safety reports (SN 033 and 040)

BRIEF DESCRIPTION OF REPRESENTATIVE SIGNIFICANT ACTIVITIES DURING THE REGULATORY PERIOD FOR FOSAPREPITANT

Reg Number	Compound ID	Filing Date	Serial Number	Activity	Description
48,924	0517	12/18/1997	"0046"	Protocol Amendment - Change in Protocol	This amendment provides for revisions to the title, patient definition, study design and laboratory supplies sections that are applicable to sites in France ONLY.
48,924	0517	1/7/1998	"0047"	Protocol Amendment - Change in Protocol	This complete amendment incorporates the changes previously made in amendment 007-001 and includes the following new changes: Pages iii, 48-50; Pages iv, 35-36; Page v; Page 30 (i) & (k); Page 31 (p); Appendix 10
50,283	0869	2/11/1998	"0060"	Information Amendment - Clinical	Information Amendment - Clinical (Protocol No. 007)
50,283	0869	3/6/1998	"0061"	Information Amendment - Clinical	Information Amendment - Clinical
48,924	0517	3/10/1998	"0049"	Protocol Amendment - New Protocol	A Single-Period Study in Healthy Subjects to Investigate Mass Balance Following CL-758,298 I.V./Protocol 010
50,283	0869	3/10/1998	"0062"	Protocol Amendment - New Protocol	Protocol Amendment - New Protocol (Protocol No. 022)
50,283	0869	3/11/1998	"0063"	Information Amendment - Chemistry/Microbiology (CMC)	Information Amendment Chemistry, Manufacturing and Control (Protocol Nos. 021,022)
50,283	0869	3/12/1998	"0064"	Information Amendment - Chemistry/Microbiology (CMC)	Information Amendment Chemistry, Manufacturing and Control (Protocol No. 022)
50,283	0869	4/1/1998	"0065"	Protocol Amendment - New Protocol	PROTOCOL AMENDMENT - NEW PROTOCOL (Protocol No. 024)
50,283	0869	4/13/1998	"0066"	Information Amendment - Chemistry/Microbiology (CMC)	Informational Amendment - Chemistry, Manufacturing and Control
48,924	0517	5/4/1998	"0050"	Protocol Amendment - Change in Protocol	Amendments to Appendices 5 & 6; and Section E- Study Design
48,924	0517	5/6/1998	"0051"	Protocol Amendment - Change in Protocol	This amendment provides for revisions to the Clinical and Administrative sections of the protocol to reflect the inclusion of up to 150 patients in the study.
50,283	0869	5/7/1998	"0067"	Protocol Amendment - Change in Protocol	Protocol Amendment - Change in Protocol (Protocol No. 016-01)
50,283	0869	6/10/1998	"0070"	Information Amendment - Chemistry/Microbiology (CMC)	Information Amendment - Chemistry, Manufacturing and Control
50,283	0869	6/10/1998	"0069"	Protocol Amendment - New Protocol	Protocol Amendment - New Protocol (Protocol No. 026)
50,283	0869	6/24/1998	"0072"	Protocol Amendment - New Protocol	Protocol Amendment - New Protocol (Protocol No. 029)
50,283	0869	6/25/1998	"0071"	Protocol Amendment - Change in Protocol	Protocol Amendment - Change in Protocol (Protocol No. 024)
50,283	0869	7/15/1998	"0073"	Information Amendment - Chemistry/Microbiology (CMC)	Information Amendment - Chemistry, Manufacturing and Control
50,283	0869	7/22/1998	"0074"	Protocol Amendment - Change in Protocol	Protocol Amendment Change in Protocol (Protocol No. 022 01)
50,283	0869	7/23/1998	"0075"	Information Amendment - Pharmacology/Toxicology	Information Amendment PharmacologyIToxicology
50,283	0869	8/5/1998	"0077"	Annual Report	IND Annual Report
50,283	0869	8/13/1998	"0078"	Information Amendment - Clinical	Information Amendment Clinical (Revised CIB)
50,283	0869	8/24/1998	"0079"	Protocol Amendment - Change in Protocol	Protocol Amendment Change in Protocol (Protocol No. 022 02)
50,283	0869	10/14/1998	"0080"	Protocol Amendment - Change in Protocol	Protocol Amendment - Change In Protocol (Protocol No. 008)
50,283	0869	10/30/1998	"0081"	Information Amendment - Pharmacology/Toxicology	Information Amendment Pharmacology/Toxicology
50,283	0869	11/3/1998	"0082"	Information Amendment - Pharmacology/Toxicology	Information Amendment Pharmacology/Toxicology/Dose Selection for Carcinogenicty Studies
50,283	0869	11/23/1998	"0083"	Protocol Amendment - New Protocol	Protocol Amendment - New Protocol (Protocol No. 010)

BRIEF DESCRIPTION OF REPRESENTATIVE SIGNIFICANT ACTIVITIES DURING THE REGULATORY PERIOD FOR FOSAPREPITANT

Reg Number	Compound ID	Filing Date	Serial Number	Activity	Description
50,283	0869	12/4/1998	"0084"	Information Amendment - Pharmacology/Toxicology	Information Amendment Pharmacology/Toxicology
50,283	0869	12/10/1998	"0085"	Information Amendment - Chemistry/Microbiology (CMC)	Informational Amendment - Chemistry, Manufacturing and Control
48,924	0517	1/6/1999	"0057"	Annual Report	Annual IND Progress Report 9/29/97-9/28/98
50,283	0869	1/18/1999	"0086"	Information Amendment - Clinical	Information Amendment- Clinical
50,283	0869	1/20/1999		Incoming Agency Correspondence	FAXed FDA minutes of FDA ECAC internal meeting
50,283	0869	2/9/1999		Incoming Agency Correspondence	FDA Response
50,283	0869	2/11/1999	"0087"	Information Amendment - Pharmacology/Toxicology	Information Amendment-Pharm/Tox
50,283	0869	2/22/1999	"0088"	Other/Meeting Information (other than Background Package)	General Correspondence Request for Meeting
50,283	0869	3/2/1999	"0089"	Response to FDA Request for Information	Response to Agency Request regarding rats and mice
50,283	0869	3/3/1999		Incoming Agency Correspondence	FDA FAX confirmation of EOPII mtg 4-14-99
48,924	0517	3/10/1999	"0058"	General Correspondence	Response to comments received from the Agency dated 8/25/98 pertaining to Protocol 007-04
50,283	0869	3/12/1999	"0090"	Other/Meeting Information (other than Background Package)	Request for Meeting
50,283	0869	3/18/1999	"0091"	Other/Meeting Information (other than Background Package)	End of Phase II Background Package
50,283	0869	5/14/1999		Incoming Agency Correspondence	End of Phase II Meeting Minutes
50,283	0869	6/4/1999	"0092"	Protocol Amendment - New Protocol	Protocol Amendment-New Protocol Request for Comment (Protocol No. 040)
48,924	0517	6/7/1999	"0059"	Protocol Amendment - Change in Protocol	In the Clinical Supplies section, wording in paragraph 5 was changed to accurately reflect how replacement subjects were handled
50,283	0869	6/8/1999	"0093"	Annual Report	Annual IND Progress Report
50,283	0869	6/11/1999	"0094"	Response to FDA Request for Information	Faxed published article
50,283	0869	6/14/1999	"0095"	Information Amendment - Chemistry/Microbiology (CMC)	Information Amendment-Chemistry, Manufacturing and Control
50,283	0869	6/28/1999	"0097"	General Correspondence	Submit 2 missing pages from protocol 040 (SN 092)
50,283	0869	6/30/1999	"0096"	Response to FDA Request for Information	information on AEs from MK-0869
50,283	0869	7/8/1999	"0098"	Protocol Amendment - New Protocol	Protocol Amendment - New Protocol (Protocol No. 041)
50,283	0869	7/12/1999	"0099"	Other/Meeting Information (other than Background Package)	MRL revisions to FDA minutes EOPII mtg 4-14-99
50,283	0869	7/29/1999	"0100"	Response to FDA Request for Information	Response to FDA Request for Information
50,283	0869	8/16/1999	"0101"	Protocol Amendment - New Protocol	Protocol Amendment-New Protocol (Protocol No. 043)
50,283	0869	8/20/1999		Incoming Agency Correspondence	FDA response to MRL meeting minutes revisions sent 7-12 99
50,283	0869	9/2/1999		Incoming Agency Correspondence	FDA Correspondence (Protocol No. 040)
50,283	0869	9/17/1999	"0103"	Protocol Amendment - New Protocol	Protocol Amendment - New Protocol (Protocol No. 044-00)
50,283	0869	9/21/1999	"0104"	Information Amendment - Chemistry/Microbiology (CMC)	Informational Amendment-Chemistry, Manufacturing and Control
50,283	0869	9/28/1999	"0106"	Information Amendment - Clinical	Informational Amendment-Clinical
50,283	0869	9/28/1999	"0108"	Information Amendment - Pharmacology/Toxicology	INFORMATION AMENDMENT-PHARMACOLOGY/TOXICOLOGY
50,283	0869	9/28/1999	"0107"	Protocol Amendment - Change in Protocol	Protocol Amendment-Change in Protocol (Protocol No. 040)
50,283	0869	10/15/1999	"0110"	Protocol Amendment - New Protocol	Protocol Amendment-New Protocol (Protocol No. 046)
48,924	0517	10/29/1999	"0060"	Annual Report	Annual IND Progress Report 9/29/98-9/28/99
50,283	0869	11/10/1999	"0111"	General Correspondence	Request for FDA concurrence on oral carco mice study proposal
50,283	0869	12/6/1999	"0113"	Protocol Amendment - Change in Protocol	Protocol Amendment - Change in Protocol (Protocol No. 041-00)

BRIEF DESCRIPTION OF REPRESENTATIVE SIGNIFICANT ACTIVITIES DURING THE REGULATORY PERIOD FOR FOSAPREPITANT

Reg Number	Compound ID	Filing Date	Serial Number	Activity	Description
50,283	0869	12/7/1999		Incoming Agency Correspondence	FDA response to 11-10-99 proposal
50,283	0869	1/6/2000	"0114"	Protocol Amendment - Change in Protocol	Protocol Amendment - Change in Protocol (Protocol 040-02)
50,283	0869	1/7/2000	"0115"	Response to FDA Request for Information	Response on pharm/tox issues rec'd 8-20-99
50,283	0869	1/12/2000	"0116"	Information Amendment - Chemistry/Microbiology (CMC)	Information Amendment Chemistry, Manufacturing and Control
50,283	0869	1/17/2000	"0117"	Protocol Amendment - Change in Protocol	Protocol Amendment - Change in Protocol (Protocol 041-01)
50,283	0869	2/7/2000	"0119"	Protocol Amendment - Change in Protocol	Protocol Amendment - Change in Protocol (040-02)
50,283	0869	3/29/2000		Incoming Agency Correspondence	Response to series of pharm/tox issues
50,283	0869	4/12/2000	"0123"	Information Amendment - Chemistry/Microbiology (CMC)	Information Amendment Chemistry, Manufacturing and Control
50,283	0869	5/12/2000	"0131"	Response to FDA Request for Information	Response to FDA Comments (March 29, 2000)
50,283	0869	5/25/2000	"0134"	Protocol Amendment - New Protocol	Protocol Amendment-New Protocol (Protocol 048-00)
50,283	0869	6/1/2000	"0136"	Annual Report	Annual IND Progress Report
50,283	0869	6/7/2000	"0137"	Protocol Amendment - Change in Protocol	Protocol Amendment - Change in Protocol (Protocol 044-01)
50,283	0869	6/9/2000	"0138"	Protocol Amendment - Change in Protocol	Protocol Amendment - Change in Protocol (Protocol 048-00, R 01-Jun-2000)
50,283	0869	7/21/2000	"0142"	Other/Meeting Information (other than Background Package)	Request for Meeting
50,283	0869	8/2/2000	"0144"	Information Amendment - Clinical	Information Amendment - Clinical
50,283	0869	8/4/2000		Incoming Agency Correspondence	FDA Correspondence (FAX)/Meeting Confirmation
50,283	0869	8/11/2000	"0146"	Information Amendment - Pharmacology/Toxicology	Information Amendment - Pharmacology/Toxicology
50,283	0869	8/15/2000	"0149"	Information Amendment - Chemistry/Microbiology (CMC)	Information Amendment - Chemistry, Manufacturing and Control
50,283	0869	8/15/2000	"0147"	Protocol Amendment - New Protocol	Protocol Amendment - New Protocol (Protocol No. 049-00)
50,283	0869	9/5/2000	"0150"	Other/Background Package	End-of-Phase II Background Package
50,283	0869	9/15/2000	"0152"	Other/Background Package	End-of-Phase II Background Package Addendum
50,283	0869	9/20/2000	"0153"	Information Amendment - Chemistry/Microbiology (CMC)	Information Amendment - CMC (KYTRIL)
50,283	0869	9/20/2000	"0154"	Protocol Amendment - New Protocol	Protocol Amendment -New Protocol (Protocol No. 050-00)
50,283	0869	9/26/2000	"0155"	General Correspondence	General Correspondence (Re: IA-C, Serial 149, August 15, 2000)
50,283	0869	9/28/2000	"0156"	Protocol Amendment - Change in Protocol	Protocol Amendment - Change in Protocol (Protocol No. 049-00)
50,283	0869	9/29/2000	"0157"	Protocol Amendment - Change in Protocol	Protocol Amendment - Change in Protocol (R-Date 11 SEP 00) (Protocol No. 049)
50,283	0869	10/9/2000	"0158"	General Correspondence	notification of trademark adoption and request for FDA review
50,283	0869	10/18/2000	"0161"	Other/Meeting Information (other than Background Package)	General Correspondence (Slides: End-of-Phase II Meeting)
50,283	0869	10/19/2000	"0163"	General Correspondence	Revised trademark review
50,283	0869	10/19/2000	"0162"	Information Amendment - Chemistry/Microbiology (CMC)	Information Amendment - Chemistry, Manufacturing and Control
50,283	0869	10/20/2000		Incoming Agency Correspondence	End-of-Phase 2 FDA Meeting Minutes
50,283	0869	10/26/2000	"0164"	General Correspondence	Update to trademark review
50,283	0869	10/27/2000	"0165"	Other/Special Protocol Assessment	Request for Special Protocol (Protocol 052-00)
50,283	0869	11/3/2000	"0166"	Protocol Amendment - New Protocol	Protocol Amendment - New Protocol (Protocol No. 051-00)
50,283	0869	11/6/2000	"0167"	Protocol Amendment - Change in Protocol	Protocol Amendment - Change in Protocol (Protocol No. 049 / R 13OCT2000)
50,283	0869	11/7/2000	"0168"	Protocol Amendment - Change in Protocol	Protocol Amendment - Change in Protocol (Protocol 049 / R20OCT2000)
48,924	0517	11/10/2000	"0062"	Annual Report	Annual IND Progress Report 9/29/99-9/28/00

BRIEF DESCRIPTION OF REPRESENTATIVE SIGNIFICANT ACTIVITIES DURING THE REGULATORY PERIOD FOR FOSAPREPITANT

Reg Number	Compound ID	Filing Date	Serial Number	Activity	Description
50,283	0869	11/14/2000	"0170"	General Correspondence	General Correspondence AE Waiver Request
50,283	0869	11/15/2000	"0171"	Information Amendment - Chemistry/Microbiology (CMC)	Information Amendment - Chemistry, Manufacturing and Controls
50,283	0869	11/22/2000	"0173"	General Correspondence	Missing serial number clarification
50,283	0869	12/5/2000	"0174"	Protocol Amendment - New Protocol	Protocol Amendment New Protocol (Protocol No. 053-00)
50,283	0869	12/12/2000	"0177"	General Correspondence	Clarification of special protocol assessment (052-00)
50,283	0869	12/14/2000		Incoming Agency Correspondence	FDA Meeting Minutes 12Dec00 Executive Carcinogenesis Assessment Committee (ECAC)
50,283	0869	1/3/2001		Incoming Agency Correspondence	Comments on pharm/tox studies (SN 146)
50,283	0869	1/5/2001		Incoming Agency Correspondence	FDA Correspondence (Re: Safety Reporting Protocol 052-00)
50,283	0869	1/8/2001	"0181"	Protocol Amendment - Change in Protocol	Protocol Amendment Change In Protocol
50,283	0869	2/5/2001	"0182"	Protocol Amendment - Change in Protocol	Protocol Amendment - Change in Protocol (Protocol 049)
50,283	0869	3/14/2001	"0188"	Information Amendment - Pharmacology/Toxicology	Information Amendment Pharmacology/Toxicology (Revised Report TT#97-737-0)
50,283	0869	3/16/2001	"0190"	Information Amendment - Clinical	Information Amendment - Clinical
50,283	0869	3/21/2001	"0192"	Response to FDA Request for Information	Resp to pharm/tox request of 1-3-01
50,283	0869	3/29/2001	"0193"	Information Amendment - Clinical	Information Amendment - Clinical Statistical Data Analysis Plan (DAP) Protocol No. 040/042
50,283	0869	4/10/2001		Incoming Agency Correspondence	FDA Comments (March 21, 2001/ Serial No. 192)
50,283	0869	4/11/2001	"0194"	Protocol Amendment - New Protocol	Protocol Amendment New Protocol (Protocol 056-00)
50,283	0869	4/26/2001		Incoming Agency Correspondence	FDA Response (Protocol No. 052-00 Submitted October 27, 2000/Serial No. 165)
50,283	0869	5/9/2001	"0198"	Other/Meeting Information (other than Background Package)	Request for Meeting (ECAC Issues)
50,283	0869	5/9/2001	"0197"	Protocol Amendment - New Protocol	Protocol Amendment - New Protocol
50,283	0869	5/11/2001		Incoming Agency Correspondence	FDA Response (May 9, 2001 Request for Meeting Letter)
50,283	0869	5/11/2001	"0199"	Protocol Amendment - Change in Protocol	Protocol Amendment Change In Protocol (Protocol 052)
50,283	0869	6/6/2001	"0200"	Information Amendment - Clinical	Information Amendment - Clinical (Revised CIB, R-24-Oct-2000)
50,283	0869	6/7/2001	"0201"	Annual Report	Annual IND Progress Report
50,283	0869	6/8/2001	"0202"	Response to FDA Request for Information	Desk copy of IA-C to IND 54,485 (dated 6-8-01)
50,283	0869	6/29/2001	"0204"	Protocol Amendment - Change in Protocol	Protocol Amendment - Change in Protocol (Protocol No. 057, R-13Jun2001)
50,283	0869	7/6/2001	"0206"	General Correspondence	Clarify discrepant serial number
50,283	0869	7/18/2001	"0208"	Response to FDA Request for Information	Response to FDA Comments (April 30, 2001)
50,283	0869	8/10/2001	"0209"	Information Amendment - Clinical	Information Amendment - Clinical (D.S.I. Correspondence 20Mar 2001, Navari)
50,283	0869	8/20/2001	"0211"	Protocol Amendment - New Protocol	Protocol Amendment - New Protocol (Protocol No. 064-00)
50,283	0869	9/7/2001	"0215"	Protocol Amendment - Change in Protocol	Protocol Amendment - Change in Protocol (Protocol No. 064-00, R 15AUG2001)
50,283	0869	11/14/2001	"0230"	Information Amendment - Chemistry/Microbiology (CMC)	Chemistry, Manufacturing and Controls (ZOFRAN (ondansetron hydrochloride) Injection)
50,283	0869	11/14/2001	"0229"	Protocol Amendment - Change in Protocol	Protocol Amendment - Change in Protocol (Protocol 052-02, Site Specific Amendment)
48,924	0517	11/16/2001	"0064"	Annual Report	IND Annual Progress Report
50,283	0869	11/28/2001	"0231"	Other/Meeting Information (other than Background Package)	Request for Pre-NDA Meeting
50,283	0869	12/10/2001	"0234"	Response to FDA Request for Information	response to trademark issues
50,283	0869	12/17/2001		Incoming Agency Correspondence	FDA Correspondence (Pre-NDA Meeting)
50,283	0869	12/18/2001	"0236"	General Correspondence	General Correspondence (MEC Data in Filing)

BRIEF DESCRIPTION OF REPRESENTATIVE SIGNIFICANT ACTIVITIES DURING THE REGULATORY PERIOD FOR FOSAPREPITANT

Reg Number	Compound ID	Filing Date	Serial Number	Activity	Description
50,283	0869	12/18/2001	"0237"	Information Amendment - Clinical	Information Amendment - Clinical Data Analysis Plan (Protocol 052/054)
50,283	0869	12/18/2001	"0235"	Protocol Amendment - Change in Protocol	Change in Protocol (Protocol No. 051-00 R-Dates 26-Nov-2001 and 11-Dec-2001)
50,283	0869	1/4/2002	"0238"	Other/Background Package	Pre-NDA Background Package (January 22, 2002 Meeting)
50,283	0869	1/9/2002		Incoming Agency Correspondence	FDA Correspondence (pre NDA Meeting Confirmation January 22, 2002)
50,283	0869	1/15/2002	"0240"	Other/Meeting Information (other than Background Package)	Pre-NDA Meeting January 22, 2002 (MRL Meeting Attendees List)
50,283	0869	1/15/2002	"0241"	Protocol Amendment - Change in Protocol	Change in Protocol (Protocol 052-02, Site Specific Amendment, R20-Dec-2001)
50,283	0869	1/17/2002		Incoming Agency Correspondence	FDA Response (Pre-NDA Background Package)
50,283	0869	1/17/2002		Incoming Agency Correspondence	FDA Fax (Pre-NDA Meeting January 22,2002) Meeting Room Change
50,283	0869	1/29/2002		Incoming Agency Correspondence	FDA Correspondence (Proposed Tradename, EMEND)
50,283	0869	2/5/2002	"0242"	Protocol Amendment - Change in Protocol	Protocol Amendment - Change in Protocol (Protocol 051-01, Worldwide Protocol)
50,283	0869	2/11/2002		Incoming Agency Correspondence	FDA Correspondence (Pre-NDA Meeting Minutes)
50,283	0869	2/15/2002	"0245"	Response to FDA Request for Information	Response to January 29, 2002 FDA Comments on Proposed Tradename, Emend
50,283	0869	3/12/2002	"0248"	Information Amendment - Clinical	Information Amendment - Clinical (Revised Data Analysis Plan - Protocols 052/054)
50,283	0869	3/12/2002	"0247"	Protocol Amendment - Change in Protocol	Protocol Amendment - Change in Protocol (Protocols 052-01 and 052-02)
50,283	0869	3/21/2002	"0251"	Other/Meeting Information (other than Background Package)	Request for Meeting Chemistry, Manufacturing and Controls
50,283	0869	4/1/2002		Incoming Agency Correspondence	FDA Correspondence (Tradename EMEND)
50,283	0869	4/10/2002		Incoming Agency Correspondence	FDA Correspondence (May 13, 2002 CMC Meeting Confirmation)
50,283	0869	4/18/2002	"0255"	Response to FDA Request for Information	Response to FDA Request for Information (SASxpt File Example)
50,283	0869	4/19/2002	"0256"	General Correspondence	General Correspondence (SASxpt Files CSR018) Response Requested
50,283	0869	5/1/2002	"0257"	Response to FDA Request for Information	Response to FDA Request (MRL Slides Presented: Pre-NDA Meeting January 22, 2002)
50,283	0869	6/4/2002	"0258"	Annual Report	IND Annual Progress Report
50,283	0869	6/14/2002	"0259"	Information Amendment - Chemistry/Microbiology (CMC)	Information Amendment - Chemistry, Manufacturing and Controls (ZOFRAN 8mg Tablets)
50,283	0869	6/18/2002	"0260"	Protocol Amendment - New Protocol	Protocol Amendment - New Protocol (Protocol 076)
50,283	0869	6/25/2002	"0261"	Other (specify in description)	EMEND Trademark Appeal/Request for FDA Response
50,283	0869	6/27/2002	"0262"	Response to FDA Request for Information	Response to FDA Request for Information Pediatric Program
50,283	0869	8/9/2002	"0264"	Other/Meeting Information (other than Background Package)	General Correspondence (May 13, 2002 CMC Meeting Cancellation)
50,283	0869	8/13/2002		Incoming Agency Correspondence	Notice re: CTDB for Protocol 076 (sub 6-18-02, SN 260)
50,283	0869	8/14/2002	"0265"	Protocol Amendment - New Protocol	Protocol Amendment - New Protocol (Protocol 071)
21-549	0869	8/20/2002		User Fee Letter	Prescription Drug User Fee - User Fee ID No. 4403 (Original NDA-CINV)
50,283	0869	8/22/2002		Other/Meeting Information (other than Background Package)	Outgoing official FAX confirm of MRL/FDA teleconf on 8-23-02 to discuss trademark
50,283	0869	9/23/2002	"0267"	Information Amendment - Chemistry/Microbiology (CMC)	Information Amendment - CMC (Protocol No. 071)
21-549	0869	9/30/2002		Original Application	Original New Drug Application: Request for Priority ReviewChemotherapy-Induced Nausea and Vomiting (CINV)

BRIEF DESCRIPTION OF REPRESENTATIVE SIGNIFICANT ACTIVITIES DURING THE REGULATORY PERIOD FOR FOSAPREPITANT

Reg Number	Compound ID	Filing Date	Serial Number	Activity	Description
50,283	0869	10/14/2002	"0268"	Information Amendment - Clinical	Information Amendment - Clinical (Revised CIB, 13 Aug 2002)
50,283	0869	10/16/2002	"0269"	Response to FDA Request for Information	Response to FDA Request for Information [MRL Meeting Minutes August 23,200 FDA Teleconference]
50,283	0869	10/17/2002	"0270"	General Correspondence	General Correspondence [Formal Dispute Resolution Request]
50,283	0869	10/18/2002		Incoming Agency Correspondence	FDA Correspondence (Pediatric Plans)
21-549	0869	10/18/2002		Other (specify in description)	Formal Dispute Resolution Request, copy of October 17, 2002 submission
50,283	0869	10/21/2002		Incoming Agency Correspondence	Notice re: CTDB for Protocol 071 (sub 8-14-02, SN 265)
21-549	0869	10/25/2002		Incoming Agency Correspondence	FDA Acknowkledgement Letter (Formal Dispute Resolution Request)
50,283	0869	10/25/2002		Incoming Agency Correspondence	FDA Acknowledgement Letter (Formal Dispute Resolution Request)
50,283	0869	10/25/2002	"0272"	Information Amendment - Chemistry/Microbiology (CMC)	Information Amendment - Chemistry, Manufacturing and Controls
50,283	0869	10/25/2002	"0271"	Protocol Amendment - New Protocol	Protocol Amendment - New Protocol (Protocol No. 081-00)
21-549	0869	10/28/2002		Incoming Agency Correspondence	FDA Request for Information (fax) (Chemistry, Manufacturing & Controls)
21-549	0869	10/30/2002		Incoming Agency Correspondence	FDA Correspondence (EMEND Tradename)
21-549	0869	11/5/2002		Other/Response to Request for Information	Updated information for 356h form
21-549	0869	11/8/2002		Incoming Agency Correspondence	FDA Acknowledgement (Original NDA Letter)
21-549	0869	11/8/2002		Incoming Agency Correspondence	FDA Request for Information (Statistics / Safety Assessment)
21-549	0869	11/19/2002		Other/Response to Request for Information	Response to FDA Request November 8, 2002
21-549	0869	11/22/2002		Other/Response to Request for Information	Response to FDA Request for Information (FDA Request 08Nov2002)
21-549	0869	11/25/2002		Other/Response to Request for Information	Response to FDA Request November 8, 2002
48,924	0517	11/26/2002	"0065"	Annual Report	IND Annual Progress Report
50,283	0869	12/2/2002	"0274"	Protocol Amendment - Change in Protocol	Protocol Amendment - Change in Protocol (Protocol 081-00 R22OCT2002)
21-549	0869	12/3/2002		Incoming Agency Correspondence	FDA Request for Information (CMC)
21-549	0869	12/27/2002		Other/Response to Request for Information	CMC Response to December 3, 2002 FDA Comments
21-549	0869	1/3/2003		Incoming Agency Correspondence	FDA Request for Information (Clinical)
21-549	0869	1/6/2003		Other/Meeting Information (other than Background Package)	Pre ACM Meeting Request to discuss ACM Background Package
21-549	0869	1/7/2003		Other/Safety Update Report (SUR)	Includes CSR 076, preliminary data for 051, along with associated label updates, Item 11.
21-549	0869	1/8/2003		Other/Response to Request for Information	Response to 03Jan2003 Clinical Info Request for stat comparison of pts w/inc LFTs 052 054
21-549	0869	1/9/2003		Incoming Agency Correspondence	FDA Correspondence (Pre-ACM Meeting Confirmation)
21-549	0869	1/15/2003		Other/Background Package	DRAFT Advisory Committee Background Package for PreACM Meeting
21-549	0869	1/16/2003		Other/Response to Request for Information	Response to January 9, 2003 FDA Request for Info, List of MRL Attendees & Questions
21-549	0869	1/22/2003		Other/Response to Request for Information	09Jan2003 FDA Request - Updated List of MRL Attendees and additional question for PreACM Mtg
21-549	0869	1/23/2003		Incoming Agency Correspondence	FDA Comments/Recommendations (Background Package Draft dated 15Jan2003)
21-549	0869	1/23/2003		Incoming Agency Correspondence	FDA Request for Information (Clinical)

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Reg Number	Compound ID	Filing Date	Serial Number	Activity	Description
21-549	0869	1/27/2003		Other/DSI Request	NDA DSI requested site info for 052-032 and 052-057
21-549	0869	1/30/2003		Incoming Agency Correspondence	FDA Request for Information (Clinical)
21-549	0869	1/31/2003		Incoming Agency Correspondence	FDA Correspondence (Pre-ACM Meeting Attendee Confirmation)
21-549	0869	2/3/2003		Other/Background Package	Final Advisory Committee Background Information for March 6, 2003 ACM with Gastrointestinal Drugs Advisory Committee (Available for Public Disclosure Without Redaction).
21-549	0869	2/6/2003		Incoming Agency Correspondence	FDA Request for Information (Statistical)
21-549	0869	2/9/2003		Incoming Agency Correspondence	FDA Federal Register Notice (March 6, 2003)
21-549	0869	2/10/2003		Incoming Agency Correspondence	FDA ACM Background Information (From Division of Information Disclosure)
21-549	0869	2/10/2003		Other (specify in description)	General Correspondence Notification of data integrity MRL audit of Dr. Campos' site - Argentina
21-549	0869	2/12/2003		Other (specify in description)	Transfer of Responsibilities: Sanders to Aurecchia
21-549	0869	2/12/2003		Other/Response to Request for Information	Jan 30, 2003 Request Re: Neutropenia
21-549	0869	2/12/2003		Other/Response to Request for Information	Response to February 6, 2003 FDA Statistical Request. Part 1 of response providing dataset for Dr. Wen Jen Chen
21-549	0869	2/12/2003		Other/Response to Request for Information	Response to January 23, 2003 Clinical Information Request
21-549	0869	2/12/2003		Other/Response to Request for Information	Response to ACM Secretary, T. Perez, request for listing of CINV specific investigators
21-549	0869	2/14/2003		Other/Response to Request for Information	Response to February 6, 2003 Statistical Request Part 2 (analyses and programs)
21-549	0869	2/20/2003		Incoming Agency Correspondence	FDA Correspondence (January 24, 2003 PreACM Meeting Minutes)
21-549	0869	2/20/2003		Other (specify in description)	Response to FDA Background Information - ACM
21-549	0869	2/27/2003		Amendment to Pending Application	Labeling (Item 2) Amendment containing minor changes in the Container Labeling and Complimentary Samples Sections of the NDA
50,283	0869	2/27/2003	"0279"	Protocol Amendment - Change in Protocol	Protocol Amendment - Change in Protocol (Protocol No. 071-02)
21-549	0869	3/4/2003		Incoming Agency Correspondence	FDA Request for Information (Clinical Request)
21-549	0869	3/11/2003		Other/Response to Request for Information	March 4, 2003 Clinical Request clarifying that our studies were conducted per GCPs
21-549	0869	3/12/2003		Incoming Agency Correspondence	FDA Markup of Proposed Labeling (Fax)
21-549	0869	3/14/2003		Other/Meeting Information (other than Background Package)	Additional Slides Shown at 06Mar2003 ACM. Available for Public Disclosure without Redaction
21-549	0869	3/17/2003		Amendment to Pending Application	Draft Labeling - Response to FDA Mockup of EMEND Label received via facsimile on March 12, 2003
21-549	0869	3/17/2003		Incoming Agency Correspondence	FDA CMC/Labeling Information Request (facsimile)
21-549	0869	3/17/2003		Incoming Agency Correspondence	FDA Mark-up of MRL Proposed Labeling Dated March 17, 2003 (Color copy received via e-mail)
21-549	0869	3/17/2003		Incoming Agency Correspondence	FDA Mark-up of MRL Proposed Labeling Dated March 17, 2003 (facsimile)
21-549	0869	3/18/2003		Incoming Agency Correspondence	FDA Response to MRL USPC 17Mar2003 Counterproposal (received via e-mail March 18, 2003)
50,283	0869	3/18/2003	"0281"	Information Amendment - Clinical	Information Amendment - Clinical (Change of Addresses, Protocol 071)
21-549	0869	3/18/2003		Other/Response to Request for Information	Proposed Post-Marketing Risk Management Program in Response to October 30, 2003 FDA Request
21-549	0869	3/19/2003		Amendment to Pending Application	Response to FDA Proposed Labeling Dated March 18, 2003
21-549	0869	3/20/2003		Amendment to Pending Application	MRL Proposed Labeling with updates per teleconference March 20, 2003

BRIEF DESCRIPTION OF REPRESENTATIVE SIGNIFICANT ACTIVITIES DURING THE REGULATORY PERIOD FOR FOSAPREPITANT

Reg Number	Compound ID	Filing Date	Serial Number	Activity	Description
21-549	0869	3/20/2003		Amendment to Pending Application	MRL Proposed Patient Package Insert per FDA's version dated March 17, 2003
21-549	0869	3/20/2003		Other/Response to Request for Information	CMC/Labeling Information Request dated March 17, 2003
21-549	0869	3/21/2003		Amendment to Pending Application	Revised Labeling (PI & PPI) per discussions during March 21, 2003 Teleconference
21-549	0869	3/21/2003		Other/Post Marketing Commitment	Phase IV Commitments
50,283	0869	3/21/2003	"0283"	Response to FDA Request for Information	Response to Request (10-18-2002 FDA Comments / Recommendations on Proposed Pediatric Program)
21-549	0869	3/24/2003		Amendment to Pending Application	Labeling Updates to Product Circular per Teleconference March 24, 2003
21-549	0869	3/26/2003		Incoming Agency Correspondence	Approval Letter. March 26, 2003 letter received via facsimile. Clean copy received via email.
21-549	0869	3/26/2003		Incoming Agency Correspondence	FDA Approval Letter, fax copy
21-549	0869	3/26/2003		Other/Post Marketing Commitment	Phase IV Commitments - updates to #2 and #4 per discussions with FDA on March 24, 2003
50,283	0869	4/8/2003	"0285"	Information Amendment - Clinical	Information Amendment - Clinical (Protocols 071, 081)
21-549	0869	4/15/2003		Incoming Agency Correspondence	FDA Approval of Safety Reporting Waiver Request
21-549	0869	4/16/2003		Amendment to Pending Application	FPL for Approved NDA 21-549
50,283	0869	4/22/2003	"0286"	Information Amendment - Clinical	Information Amendment - Clinical (Protocol No. 071)
21-549	0869	4/24/2003		Other/Patent Information	Time Sensitive Patent Information for NDA 21-549
21-549	0869	5/5/2003		Other/Meeting Information (other than Background Package)	General Correspondence containing a copy of March 3, 2003 DDMAC Meeting Minutes.
50,283	0869	5/5/2003	"0263"	Other/Meeting Information (other than Background Package)	General Correspondence (March 3, 2003 Meeting Minutes)
21-549	0869	5/7/2003		Other (specify in description)	Launch Promotion Material for EMEND submitted to DDMAC with a copy to the Division 24Apr2003
21-549	0869	5/20/2003		Other/Post Marketing Commitment	Post Marketing Study Final Report, Commitment #5.
21-549	0869	5/21/2003		CMC Supplement - PAS	Requests the extension of the expiry period from 24 months to 36 months for EMEND™
	0869	5/23/2003		Information Amendment - Clinical	Mapp 31 FDA Correspondence, Dr. Jorg Pahl, study 061-0020 and 068-0023
	0869	5/27/2003		Annual Report	Annual Report (4/10/02 - 4/9/03) w/CSR snyopsis for Prot. 049, 052, 056, 057, 064, 076
	0869	5/27/2003		Information Amendment - Clinical	IA - C Prot. 062, 066 (change of correspondence/site address)
21-549	0869	6/2/2003		Incoming Agency Correspondence	Acknowledgment Letter of Receipt, Extension of the expiry period from 24 to 36 months.
21-549	0869	6/2/2003		Incoming Agency Correspondence	FDA Acknowledgement Letter (Extension of Expiry Period)
50,283	0869	6/5/2003	"0289"	Other/Meeting Information (other than Background Package)	Minutes of DDMAC meeting March 3, 2003.
50,283	0869	6/6/2003	"0291"	Information Amendment - Clinical	071-0039, 071-0061, 071-0092, 071-0115
50,283	0869	6/25/2003	"0292"	Protocol Amendment - Change in Protocol	071-10 extension study. Protocol 071-10 to permit the option of up to 7 cycles chemo.
21-549	0869	6/27/2003		Other/Post Marketing Commitment	Post Marketing Study Correspondence, Commitment #6, regarding SDS Media and Particle Size Stab.
21-549	0869	7/3/2003		Other/Meeting Information (other than Background Package)	Request for pre-sNDA Meeting, EMEND for Moderately Emetogenic Chemotherapy
21-549	0869	7/15/2003		Incoming Agency Correspondence	Confirmation of September 4, 2003 Pre-sNDA Meeting
50,283	0869	7/15/2003	"0293"	Other/Special Protocol Assessment	P090 - Request for Special Protocol Assessment
21-549	0869	7/17/2003		Labeling Supplement - CBE	This supplement provides for editorial changes to the label.
21-549	0869	7/25/2003		Other/Periodic Adverse Drug Reaction Report (ADR)	Periodic Adverse Experience Report
50,283	0869	7/30/2003	"0295"	Information Amendment - Clinical	DAP protocol 071 MEC CDP trial. DAP to also be included within the Pre-sNDA background package

BRIEF DESCRIPTION OF REPRESENTATIVE SIGNIFICANT ACTIVITIES DURING THE REGULATORY PERIOD FOR FOSAPREPITANT

Reg Number	Compound ID	Filing Date	Serial Number	Activity	Description
21-549	0869	8/1/2003		Incoming Agency Correspondence	Request for Information. Comments on March 18, 2003 Post-Marketing Risk Management Plan
21-549	0869	8/1/2003		Other/Background Package	Pre-sNDA Background Package for September 4, 2003 Agency Meeting to discuss MEC program.
50,283	0869	8/14/2003	"0297"	Information Amendment - Clinical	IA - C Prot. 071
50,283	0869	8/19/2003	"0298"	Information Amendment - Clinical	IA- C Prot. 071
21-549	0869	8/22/2003		Incoming Agency Correspondence	Stats Information Request regarding expiry extension prior approval supplement.
50,283	0869	8/26/2003		Incoming Agency Correspondence	Acknowledgment Letter of receipt for Special Protocol Assessment (P090 PONV Study)
50,283	0869	8/29/2003		Incoming Agency Correspondence	Special Protocol Assessment Comments. Protocol 090. PONV study.
21-549	0869	9/3/2003		Incoming Agency Correspondence	FDA Responses to MRL Questions for Pre-NDA Meeting Re: MEC
21-549	0869	9/3/2003		Other/Response to Request for Information	Expiry Extension Supplement. Response to August 22, 2003 FDA Request for Information
21-549	0869	9/4/2003		Incoming Agency Correspondence	Pre-sNDA Meeting (9/4/03) Minutes Re: MEC Program
50,283	0869	9/8/2003	"0300"	Information Amendment - Clinical	Revised Confidential Informational Brochure.
50,283	0869	9/11/2003	"0303"	Information Amendment - Chemistry/Microbiology (CMC)	Supports PONV Protocol 090. 40 mg and 125 mg Aprepitant Capsules, Zofran IV/pbo 4 mg.
50,283	0869	9/11/2003	"0302"	Information Amendment - Clinical	Prot. 071
50,283	0869	9/15/2003	"0305"	Protocol Amendment - New Protocol	090-00 (R-14Aug2003), PONV study
21-549	0869	9/22/2003		Incoming Agency Correspondence	Approval Letter. Expiry extension from 24 months to 36 months.
50,283	0869	9/24/2003	"0308"	Protocol Amendment - New Protocol	Protocol 091. Worldwide PONV study.
50,283	0869	9/24/2003	"0309"	Response to FDA Request for Information	Response to FDA Comments Regarding Special Protocol Assessment, Protocol 090
	0869	9/26/2003		Other (specify in description)	Response to FDA Request for Information
21-549	0869	9/26/2003		Other/Meeting Information (other than Background Package)	MEC Response to FDA Comments Regarding MRL's pre-sNDA Meeting Questions
21-549	0869	9/26/2003		Other/Post Marketing Commitment	Post Marketing Study Correspondence, Commitment #4, Risk Management Plan
50,283	0869	10/1/2003	"0310"	Information Amendment - Clinical	Prot. 071 - Addition of new site
21-549	0869	10/2/2003		Incoming Agency Correspondence	Meeting Minutes, 04Sep2003 MEC Pre-sNDA Meeting discussing Protocol 071
50,283	0869	10/3/2003	"0311"	Protocol Amendment - New Protocol	Protocol No. 095-00, Ondansetron Bioequivalence Study
21-549	0869	10/9/2003		Other/Post Marketing Commitment	Post Marketing Study Protocol, Commitment #3 (Protocol 094-00)
50,283	0869	10/9/2003	"0312"	Protocol Amendment - New Protocol	Protocol 094-00, Post Marketing Commitment #3.
50,283	0869	10/17/2003	"0314"	Information Amendment - Clinical	Revised Statistical Data Analysis Plan - Protocol 071, MEC study
21-549	0869	10/24/2003		Other/Periodic Adverse Drug Reaction Report (ADR)	Periodic Adverse Experience Report
50,283	0869	10/28/2003	"0315"	Protocol Amendment - Change in Protocol	095-00, rdate 23Oct2003, Ondansetron Bioequivalence Study
50,283	0869	10/29/2003	"0318"	Information Amendment - Chemistry/Microbiology (CMC)	Zofran over-encapsulated UK tablets 8 mg, Zofran US & UK 8 mg tablets.
50,283	0869	10/30/2003	"0316"	Information Amendment - Clinical	Prot. 071 - change of correspondence address
50,283	0869	11/5/2003		Incoming Agency Correspondence	Request for Information, Protocol 095-00, Ondansetron Bioequivalence Study
48,924	0517	11/10/2003	"0068"	Annual Report	I.V. (29-Sep-02 through 28-Sep-03)
50,283	0869	11/10/2003	"0319"	Response to FDA Request for Information	FDA Facsimile dated November 5, 2003 regarding protocol 095
50,283	0869	11/12/2003	"0321"	Response to FDA Request for Information	Correction to November 10, 2003, Serial No. 319.
50,283	0869	11/19/2003	"0322"	Protocol Amendment - Change in Protocol	090-01 and 091-01. PONV study revisions.
21-549	0869	11/24/2003		Other (specify in description)	"Courtesy Copy" Periodic Safety Update Report(Cover Letter only) 3/26/2003-9/25/2003

BRIEF DESCRIPTION OF REPRESENTATIVE SIGNIFICANT ACTIVITIES DURING THE REGULATORY PERIOD FOR FOSAPREPITANT

Reg Number	Compound ID	Filing Date	Serial Number	Activity	Description
21-549	0869	12/3/2003		Other/Post Marketing Commitment	Post Marketing Study Correspondence, Commitment #1 (Protocol #051)
21-549	0869	12/11/2003		Other/Post Marketing Commitment	Post Marketing Study Correspondence, Commitment #4, Risk Management Plan
	0869	1/6/2004		Incoming Agency Correspondence	Approval Letter, Supports PONV Program, 40 mg aprepitant, 14 countries
50,283	0869	1/9/2004	"0326"	Protocol Amendment - Change in Protocol	Protocol No. 090-02, PONV Site Specific PK Amendment
50,283	0869	1/9/2004	"0327"	Protocol Amendment - New Protocol	Protocol No. 098-00, CINV Induction Study
21-549	0869	1/15/2004		Incoming Agency Correspondence	Approval Letter. This CBE supplement provides for Editorial changes to the label.
50,283	0869	1/16/2004	"0328"	Information Amendment - Chemistry/Microbiology (CMC)	Stable-Labeled Midazolam for Injection
21-549	0869	1/23/2004		Other/Periodic Adverse Drug Reaction Report (ADR)	Periodic Adverse Experience Report Sept. 27, 2003 to Dec. 26, 2003
50,283	0869	2/2/2004	"0331"	Protocol Amendment - Change in Protocol	Protocol No. 094-00 rdate 16Jan2004.
50,283	0869	2/2/2004	"0332"	Protocol Amendment - Change in Protocol	Protocol No. 090-02 site specific PK amendment revisions.
50,283	0869	2/18/2004	"0333"	Information Amendment - Clinical	New Correspondence/Site Address, 071-0063
50,283	0869	2/27/2004	"0336"	General Correspondence	External Review Board Guidelines - Protocol 090
50,283	0869	2/27/2004	"0335"	Protocol Amendment - New Protocol	Protocol Number 097, Adolescent HEC Study
50,283	0869	3/2/2004	"0337"	Information Amendment - Clinical	Study Site Number 071-0108. New Site Address
50,283	0869	3/26/2004	"0342"	Information Amendment - Clinical	Data Analysis Plan Protocols 090 091.
50,283	0869	3/26/2004	"0340"	Other/IND Reference Authorization	IND Reference Authorization (non-Merck IND 67,550 / Patrick Stiff, MD)
50,283	0869	3/26/2004	"0341"	Protocol Amendment - New Protocol	Protocol Number 101-00. Vinorelbine Post-Marketing Study Commitment #2
21-549	0869	3/29/2004		Other/Post Marketing Commitment	Post-Marketing Protocol Study Correspondence, Commitment #2 (Protocol #101-00)
21-549	0869	3/31/2004		Other/Post Marketing Commitment	Post-Marketing Study Correspondence (Commitment #4, Risk Management Plan)
50,283	0869	4/8/2004	"0343"	Information Amendment - Clinical	MAPP 31 FDA Correspondence, Site 090-0024, Dr. Paul F. White
50,283	0869	4/20/2004	"0344"	Other/IND Reference Authorization	IND Cross-Reference Authroization (Dr. Paul J. Hesketh, MD/IND 69,352)
21-549	0869	4/23/2004		Other/Periodic Adverse Drug Reaction Report (ADR)	Periodic Adverse Experience Report
50,283	0869	5/7/2004		Incoming Agency Correspondence	Request for Information, Adolescent HEC Study 097 submitted 27Feb03/Pediatric Development Plan
50,283	0869	5/14/2004	"0346"	Information Amendment - Clinical	New Site Address, 090-0016
50,283	0869	5/18/2004	"0347"	Protocol Amendment - New Protocol	Protocol No. 106-00, Ondansetron 2-Period Crossover Bioequivalence Study
21-549	0869	5/19/2004		Other (specify in description)	"Courtesy Copy" Periodic Safety Update Report(Cover Letter only) 9/26/2003-3/25/2004
21-549	0869	5/21/2004		Annual Report	Capsules Annual Report (26-MAR-03 through 26-MAR-04)
21-549	0869	5/21/2004		Other/Post Marketing Commitment	Post Marketing Study Correspondence, Commitment #3 (Protocol No. 094)
21-549	0869	5/28/2004		Other/Post Marketing Commitment	Post Marketing Study Final Report, Commitment #1, Docetaxel Interaction Study
21-549	0869	6/4/2004		CMC Supplement - PAS	Change in API Chemistry (CMT Process)
50,283	0869	6/8/2004	"0348"	Annual Report	Capsules Annual Report 10-Apr-03 to 09-Apr-04
50,283	0869	6/11/2004	"0349"	Information Amendment - Chemistry/Microbiology (CMC)	Supports CMC changes related to Protocols 090 and 091.
21-549	0869	6/15/2004		Labeling Supplement - PAS	Docetaxel P051 Interaction Study Labeling Update
21-549	0869	6/16/2004		CMC Supplement - PAS	Expiry extension from the current 36 months to 48 months
21-549	0869	6/25/2004		Labeling Supplement - PAS	Hormonal Contraceptive Interaction Study (P081) Labeling Update

BRIEF DESCRIPTION OF REPRESENTATIVE SIGNIFICANT ACTIVITIES DURING THE REGULATORY PERIOD FOR FOSAPREPITANT

Reg Number	Compound ID	Filing Date	Serial Number	Activity	Description
48,924	0517	6/28/2004	"0070"	Other (specify in description)	Request for FDA Review/Comment - Does IND update require 30 day waiting period?
21-549	0869	6/28/2004		Other/Post Marketing Commitment	Post Marketing Study Correspondence (Commitment #4, Risk Management Plan)
21-549	0869	6/30/2004		Other/Response to Request for Information	Response to FDA - 48 Month Expiry Extension
50,283	0869	7/12/2004	"0351"	Information Amendment - Clinical	New Correspondence/Site/IRB addresses - 071-0116, New Site Address 090-0010
50,283	0869	7/21/2004	"0354"	Other/IND Reference Authorization	IND Cross-Ref Authorization (Joseph S. Bubalo, PharmD/IND 68,766)
21-549	0869	7/26/2004		Other/Periodic Adverse Drug Reaction Report (ADR)	Periodic Adverse Experience Report
50,283	0869	7/26/2004	"0356"	Protocol Amendment - New Protocol	Protocol No. 108-00. Aprepitant 125-mg IV Midazolam Interaction
50,283	0869	7/26/2004	"0355"	Protocol Amendment - New Protocol	Protocol No. 107-00 Aprepitant 40 mg FMC Study
48,924	0517	7/28/2004	"0071"	Initial	IND Update for CMC and Safety Assessment studies
21-549	0869	7/30/2004		Incoming Agency Correspondence	Acknowledgment Letter of receipt (Docetaxil P051 Interaction Study Labeling Update)
21-549	0869	7/30/2004		Incoming Agency Correspondence	Acknowledgment Letter of receipt (Expiry Extension to 48 months)
50,283	0869	8/2/2004	"0357"	Other/IND Reference Authorization	IND Reference Authorization (Charles L. Loprini, M.D./IND 68,480)
50,283	0869	8/2/2004		Response to FDA Request for Information	Response Re: Protocol 097-00 (Serial No. Discrepancy - see long description)
48,924	0517	8/4/2004	"0072"	Information Amendment - Pharmacology/Toxicology	3 Supportive Toxicology Reports to Summary Provided within July 28, 2004 IND Update
21-549	0869	8/11/2004		Incoming Agency Correspondence	Acknowledgment Letter of receipt (sNDAs administratively split - see Long description)
48,924	0517	8/12/2004	"0073"	Information Amendment - Clinical	Revised CIB (Edition No. 1)
50,283	0869	8/25/2004	"0359"	Protocol Amendment - Change in Protocol	Protocol 101-00(R03-Aug-2004)
21-549	0869	8/25/2004		User Fee Letter	User Fee ID No. 4831 (MEC filing)
50,283	0869	9/10/2004	"0360"	Information Amendment - Chemistry/Microbiology (CMC)	25 mg/mL suspension of L-000754030 in Water for Injection
21-549	0869	9/15/2004		Other/Pediatric Information	Proposed Pediatric Study Request
50,283	0869	9/17/2004	"0361"	Other/IND Reference Authorization	IND Reference Authorization (Luis Isola, MD IND 70,422)
21-549	0869	9/20/2004		Other/Post Marketing Commitment	Post-Marketing Study Commitment #4 - Risk Management Program
21-549	0869	9/29/2004		Efficacy Supplement	Prevention of CINV associated with moderately emetogenic chemotherapy (MEC)
21-549	0869	9/29/2004		Incoming Agency Correspondence	Approval Letter (see long description)
48,924	0869	9/29/2004	"0075"	Protocol Amendment - Change in Protocol	Protocol 011-01
50,283	0869	9/29/2004	"0364"	Protocol Amendment - Change in Protocol	Protocol 107-00(R10Sep04)
50,283	0869	9/29/2004		Incoming Agency Correspondence	Other Agency Correspondence (FDA Comments & Recommendations on SOP for ERB for P090)
21-549	0869	9/29/2004		Incoming Agency Correspondence	Approval Letter (sNDA provides for extension of the expiration dating to 48 months)
21-549	0869	9/29/2004		Other/Periodic Adverse Drug Reaction Report (ADR)	Periodic Adverse Experience Report
50,283	0869	9/29/2004	"0365"	Information Amendment - Chemistry/Microbiology (CMC)	GALEN (Dexamethasone) Tablets, 4 mg & Placebo for MK-0869 Capsules, 80 mg
50,283	0869	9/29/2004	"0366"	Protocol Amendment - Change in Protocol	Protocol No. 097 Revisions dated 14Oct2004.
50,283	0869	9/29/2004	"0367"	Information Amendment - Chemistry/Microbiology (CMC)	Placebo for GALEN Tablets, 4 mg & Change in appearance color of MK-0869 80 mg Placebo Capsules
21-549	0869	9/29/2004		Incoming Agency Correspondence	Request for Information (MEC P071 Data Request)
21-549	0869	9/29/2004		Other (specify in description)	"Courtesy Copy" Periodic Safety Update Report(Cover letter only)3/26/2004-9/25/2004

BRIEF DESCRIPTION OF REPRESENTATIVE SIGNIFICANT ACTIVITIES DURING THE REGULATORY PERIOD FOR FOSAPREPITANT

Reg Number	Compound ID	Filing Date	Serial Number	Activity	Description
48,924	0869	9/29/2004	"0076"	Annual Report	I.V. Annual Report for 9/29/03 to 9/28/04
21-549	0869	9/29/2004		Other (specify in description)	Request for Exemption to Office of Compliance (NCR packaging)
50,283	0869	9/29/2004	"0368"	Other/Meeting Information (other than Background Package)	Request for Type B meeting (PONV)
21-549	0869	9/29/2004		Incoming Agency Correspondence	Acknowledgment Letter of receipt (MEC sNDA)
21-549	0869	9/29/2004		Incoming Agency Correspondence	Acknowledgment Letter of receipt (Oral Contraceptive PK Study)
21-549	0869	9/29/2004		Labeling Supplement - PAS	Dolasetron P094 Interaction Study Labeling Update/Post-Marketing Study Final Report
21-549	0869	9/29/2004		Incoming Agency Correspondence	Acknowledgment Letter of receipt (MEC sNDA)
21-549	0869	9/29/2004		Incoming Agency Correspondence	Approval Letter (Docetaxel Interaction Study P051 Labeling Update)
50,283	0869	9/29/2004		Incoming Agency Correspondence	Other Agency Correspondence (PONV Pre-NDA Meeting Granted)
21-549	0869	12/17/2004		Other/Response to Request for Information	Stat Review Aids for MEC CSR P071
21-549	0869	12/22/2004		Incoming Agency Correspondence	Approval Letter (Hormonal Contraceptive Interaction Study (P081) Label Update)
21-549	0869	12/22/2004		Other/Post Marketing Commitment	Post-Marketing Study Commitment #4 - Risk Management Program
48,924	0517	1/4/2005	"0077"	Protocol Amendment - New Protocol	Protocol 012
21-549	0869	1/5/2005		Amendment to Pending Application	Request for Partial Waiver in Age Group < 2 years for MEC indication
21-549	0869	1/10/2005		Incoming Agency Correspondence	Request for Information (Re: NCR Packaging Exemption Request)
21-549	0869	1/18/2005		Other/Response to Request for Information	Response Re: NCR Packaging
48,924	0517	1/20/2005	"0078"	Information Amendment - Chemistry/Microbiology (CMC)	Drug Substance Update & Addition of 40 mg MK-0869 Capsule & 150 mg/vial MK-0517
21-549	0869	1/21/2005		Incoming Agency Correspondence	Acknowledgment Letter of receipt (Dolasetron Interaction Study)
21-549	0869	1/21/2005		Incoming Agency Correspondence	Pediatric Information (Waiver < 2 Years Denied, Deferral for 2 - 17 Years Granted)
21-549	0869	1/25/2005		Other/Periodic Adverse Drug Reaction Report (ADR)	Periodic Adverse Experience Report 9/27/04-12/26/04
21-549	0869	1/28/2005		Other/Safety Update Report (SUR)	MEC Safety Update Report
50,283	0869	2/2/2005	"0372"	Other/Background Package	PONV Type B (Pre-sNDA) Meeting Bkgd Pkg
48,924	0517	2/7/2005	"0079"	Protocol Amendment - Change in Protocol	Protocol 012-01
21-549	0869	2/18/2005		Other/Response to Request for Information	Response to FDA Request during February 9, 2005 Telecon re: CPSC & NCR packaging
50,283	0869	2/23/2005		Incoming Agency Correspondence	Other Agency Correspondence (PONV Pre-sNDA Meeting Responses)
48,924	0517	3/22/2005	"0081"	Other/Meeting Information (other than Background Package)	Request for Type B Meeting (Clinical Strategy for L-000758298 IV Formulation)
50,283	0869	3/24/2005	"0373"	Other/Meeting Information (other than Background Package)	PONV Feb 24, 2005 Pre-sNDA Meeting Summary
50,283	0869	3/24/2005	"0374"	Protocol Amendment - Change in Protocol	Protocol 091-02
50,283	0869	3/25/2005		Incoming Agency Correspondence	FDA Meeting Minutes from 2/24/05 PONV pre-sNDA Mtg
50,283	0869	3/29/2005	"0375"	Other/IND Reference Authorization	IND Reference Authorization (Muneer Abidi, MD / IND 71,394)
50,283	0869	3/31/2005	"0376"	Information Amendment - Clinical	Revised CIB, Edition No. 6
21-549	0869	3/31/2005		Other/Post Marketing Commitment	Post-Marketing Study Correspondence (Commitment #4, Risk Mgt Plan)
21-549	0869	4/4/2005		Amendment to Pending Application	FPL for S-004 and S-007
50,283	0869	4/12/2005	"0378"	Information Amendment - Clinical	Change in Site Info - Protocol 097
48,924	0517	4/12/2005	"0082"	Protocol Amendment - Change in Protocol	Protocol 012-02
50,283	0869	4/21/2005	"0379"	Information Amendment - Clinical	DAP for P091

BRIEF DESCRIPTION OF REPRESENTATIVE SIGNIFICANT ACTIVITIES DURING THE REGULATORY PERIOD FOR FOSAPREPITANT

Reg Number	Compound ID	Filing Date	Serial Number	Activity	Description
21-549	0869	4/25/2005		Other/Periodic Adverse Drug Reaction Report (ADR)	Periodic Adverse Experience Report 12/27/04-03/26/05
21-549	0869	4/26/2005		Incoming Agency Correspondence	Pediatric Information (FDA Recommendations for EMEND PPSR)
50,283	0869	4/27/2005	"0381"	Protocol Amendment - Change in Protocol	Protocol 097-01
48,924	0517	4/29/2005		Incoming Agency Correspondence	Other Agency Correspondence (Type C meeting to discuss Clinical Strategy scheduled for 6/9/05)
48,924	0517	5/13/2005	"0083"	Other/Background Package	Type C Meeting Background Package for June 9, 2005 Meeting
21-549	0869	5/20/2005		Other/Response to Request for Information	Response to FDA Request Re: Nausea Severity Assessment in MEC P071
21-549	0869	5/23/2005		Other/Response to Request for Information	Response to FDA Request for MS Word version of PI and Annotated PI (Dolasetron)
21-549	0869	5/24/2005		Incoming Agency Correspondence	Other Agency Correspondence (CPSC Denial of NCR Packaging)
21-549	0869	5/25/2005		Annual Report	Capsules Annual Report for 27-Mar-04 to 26-Mar-05
48,924	0517	5/25/2005	"0084"	Protocol Amendment - Change in Protocol	Protocol 012-03
50,283	0869	5/26/2005	"0382"	Annual Report	Capsules Annual Report for 10-Apr-04 to 09-Apr-05
21-549	0869	6/3/2005		Incoming Agency Correspondence	Request for Information (Info on FLIE Questionnaire Used in P071)
48,924	0517	6/8/2005		Incoming Agency Correspondence	Type C Clinical Strategy Pre-Meeting Responses
21-549	0869	6/9/2005		Incoming Agency Correspondence	Request for Information Re: P071 (MEC) Nausea Endpoint
21-549	0869	6/9/2005		Incoming Agency Correspondence	Approval Letter (Dolasetron P094 Interaction Study Label Update/PM Commitment #3 Fulfilled)
21-549	0869	6/9/2005		Incoming Agency Correspondence	Request for Information Re P071 (MEC) Breakdowns of SAEs
21-549	0869	6/9/2005		Incoming Agency Correspondence	Request for Information (Postmarketing Data)
21-549	0869	6/10/2005		Incoming Agency Correspondence	Request for Information (Postmarketing Data)
21-549	0869	6/14/2005		Other/Response to Request for Information	FDA Request for Info Re: P071 and the FLIE
21-549	0869	6/15/2005		Other/Response to Request for Information	P071 (MEC) Summary Tables for SAEs Resulting in Study Termination
48,924	0517	6/16/2005		Incoming Agency Correspondence	Meeting Minutes from 6/9/05 Clinical Strategy FDA Meeting
21-549	0869	6/16/2005		Other/Response to Request for Information	Request for Explanation Re: P071 (MEC) Study Results
21-549	0869	6/16/2005		Other/Response to Request for Information	Request for Labeling Versions of S-008 (MEC) with S-009 Included (Dolasetron)
48,924	0517	6/20/2005	"0085"	General Correspondence	Request for User Fee Guidance on CINV and PONV Submissions
21-549	0869	6/20/2005		Other/Response to Request for Information	FDA Request for Postmarketing AE Information (P071)
48,924	0517	6/27/2005	"0086"	Other/Special Protocol Assessment	Request for Special Protocol Assessment (Clinical Protocol - PONV)
48,924	0517	6/28/2005	"0087"	Other/Meeting Information (other than Background Package)	Request for FDA Meeting (To Discuss MRLs CMC Strategy for IV formulation)
48,924	0517	6/29/2005	"0088"	General Correspondence	Request for FDA Concurrence Re: QTc prolongation risk of MK-0517
48,924	0517	6/29/2005		Incoming Agency Correspondence	Other Agency Correspondence (CMC Telecon Cancellation and Advice)
48,924	0517	7/14/2005	"0089"	Information Amendment - Chemistry/Microbiology (CMC)	Updated CMC Info for 40 mg formulation & ZOFRAN Injection supplies
48,924	0517	7/14/2005	"0090"	Other/Meeting Information (other than Background Package)	MRL Summary of June 9, 2005 Clinical/CMC Strategy Meeting
48,924	0517	7/15/2005	"0091"	Other/Meeting Information (other than Background Package)	Request for Type B (Pre NDA) Meeting
48,924	0517	7/19/2005	"0092"	Information Amendment - Chemistry/Microbiology (CMC)	Update to manufacturing process description for MK-0517 drug product info

BRIEF DESCRIPTION OF REPRESENTATIVE SIGNIFICANT ACTIVITIES DURING THE REGULATORY PERIOD FOR FOSAPREPITANT

Reg Number	Compound ID	Filing Date	Serial Number	Activity	Description
21-549	0869	7/19/2005		User Fee Letter	User Fee for PONV sNDA (PD3006108)
21-549	0869	7/22/2005		Other/Response to Request for Information	Response to FDA July 12, 2005 Requests Re: MEC
21-549	0869	7/26/2005		Incoming Agency Correspondence	Other Agency Correspondence (PDUFA Goal Date Extension)
21-549	0869	7/26/2005		Other/Periodic Adverse Drug Reaction Report (ADR)	Periodic Adverse Experience Report 03/27/05-06/26/05
48,924	0517	8/4/2005	"0093"	Other (specify in description)	Request for CDER Review of Proposed Trademark
50,283	0869	8/8/2005		Incoming Agency Correspondence	Other Agency Correspondence (FDA Comments on Prevention of Adolescent CINV Study P097-01)
48,924	0517	8/10/2005		Incoming Agency Correspondence	Other Agency Correspondence (FDA Comments on Request for Special Protocol Assessment of P015)
48,924	0517	8/15/2005	"0094"	Other/Background Package	Pre-NDA (Type B) Meeting Background Package
48,924	0517	8/17/2005	"0095"	Other/Meeting Information (other than Background Package)	Request for Type A Meeting (Confirmation of Agencys Position Re: PONV Indication for MK-0517)
48,924	0517	8/23/2005		Incoming Agency Correspondence	Other Agency Correspondence (Draft Type B (Pre-NDA) Meeting Responses (CMC))
21-549	0869	8/29/2005		Efficacy Supplement	Prevention of Post-Operative Nausea and Vomiting (PONV)
48,924	0517	9/2/2005		Incoming Agency Correspondence	Meeting Minutes (8/29/05 Type B Meeting to discuss CMC issues)
48,924	0517	9/2/2005		Incoming Agency Correspondence	Other Agency Correspondence (9/8 Type A Mtg scheduled to discuss FDA's 8/10/05 SPA response)
48,924	0517	9/7/2005		Incoming Agency Correspondence	Other Agency Correspondence (FDA's Draft Response Re: P015 SPA for 9/8/05 Mtg (canceled))
48,924	0517	9/9/2005		Incoming Agency Correspondence	Other Agency Correspondence (FDA Feedback re: QTC Studies)
50,283	0869	9/13/2005	"0383"	Information Amendment - Clinical	Change in Site Info - Protocol 091-0040
48,924	0517	9/19/2005	"0096"	Protocol Amendment - Change in Protocol	Protocol 012-04
48,924	0517	9/19/2005	"0097"	Protocol Amendment - New Protocol	Protocol 015
50,283	0869	9/21/2005	"0384"	Other/IND Reference Authorization	IND Reference Authorization Letter (Steven Devine, MD - IND 70268)
48,924	0517	9/22/2005	"0099"	General Correspondence	Request for FDA Concurrence with NDA Submission Components
48,924	0517	9/22/2005	"0098"	Protocol Amendment - New Protocol	Protocol 016 - QTc study
21-549	0869	9/27/2005		Incoming Agency Correspondence	Postmarketing Commitment Update
48,924	0517	9/29/2005	"0100"	Information Amendment - Chemistry/Microbiology (CMC)	125 mg capsule, MK-0869
50,283	0869	10/3/2005	"0385"	Other/IND Reference Authorization	IND Reference Authorization Letter (Stacy Shord, PharmD - IND72029)
48,924	0517	10/6/2005		Incoming Agency Correspondence	Other Agency Correspondence (Acknowledgment of MRL's Decision to Accept FDA's SPA for Prot 015)
50,283	0869	10/13/2005		Protocol Amendment - New Protocol	Protocol 128 (RDT)
48,924	0517	10/14/2005	"0102"	General Correspondence	Type B (CMC) Meeting Summary (8/29/05)
48,924	0517	10/19/2005	"0103"	Information Amendment - Chemistry/Microbiology (CMC)	Moxifloxacin Hydrochloride, 400 mg Tablets (active & placebo)
21-549	0869	10/24/2005		Incoming Agency Correspondence	Post Marketing Commitment (MEC Study)
48,924	0517	10/24/2005	"0104"	Other/Meeting Information (other than Background Package)	Request for Type B Meeting (Pre NDA meeting for CINV and PONV)
21-549	0869	10/26/2005		Other/Periodic Adverse Drug Reaction Report (ADR)	Periodic Adverse Experience Report 06/27/05-09/26/05
21-549	0869	10/27/2005		Amendment to Pending Application	Revised Package Circular based on FDA/MRL Telecons/Label Negotiations
21-549	0869	10/27/2005		Other/Response to Request for Information	Response to Request for EMEND Container Label, EUSPC, and List of Countries with EMEND Approved
21-549	0869	10/28/2005		Incoming Agency Correspondence	Approval Letter (MEC - Moderately Emetogenic Chemotherapy); includes PM Commitment for MEC Study)

BRIEF DESCRIPTION OF REPRESENTATIVE SIGNIFICANT ACTIVITIES DURING THE REGULATORY PERIOD FOR FOSAPREPITANT

Reg Number	Compound ID	Filing Date	Serial Number	Activity	Description
21-549	0869	10/28/2005		Other/Safety Update Report (SUR)	Request for Waiver of Safety Update Report
48,924	0517	11/4/2005		Incoming Agency Correspondence	Other Agency Correspondence (FDA Acceptance of P016 - QTc Study)
21-549	0869	11/10/2005		Incoming Agency Correspondence	Acknowledgment Letter of receipt (PONV sNDA)
50,283	0869	11/17/2005	"0387"	Information Amendment - Chemistry/Microbiology (CMC)	40 mg RDT, MK-0869
48,924	0517	11/22/2005		Incoming Agency Correspondence	Other Agency Correspondence (CINV & PONV Pre-NDA Meeting Confirmation)
48,924	0517	11/22/2005	"0106"	Other/Background Package	Pre NDA Meeting Background Package
48,924	0517	11/23/2005	"0105"	Annual Report	I.V. Annual Report for 29-Sep-2004 through 28-Sep-2005.
48,924	0517	11/28/2005	"0107"	Information Amendment - Clinical	SAP for P015
50,283	0869	12/1/2005	"0388"	Protocol Amendment - Change in Protocol	Protocol 128 (R15-Nov-2005)
21-549	0869	12/7/2005		Amendment to Pending Application	Final Printed Labeling for sNDAs S-008 (MEC) & S-009 (dolasetron)
21-549	0869	12/8/2005		Labeling Supplement - PAS	Labeling Revisions Based on Additional Carcinogenicity Studies.
48,924	0517	12/13/2005		Incoming Agency Correspondence	Other Agency Correspondence (FDA Draft Responses in preparation for CINV/PONV PreNDA meeting)
48,924	0517	12/20/2005		Incoming Agency Correspondence	Request for Information (FDA Request for In Vitro information on MK-0517)
21-549	0869	12/28/2005		Other/Safety Update Report (SUR)	Safety Update Report: PONV
50,283	0869	1/6/2006	"0390"	Information Amendment - Pharmacology/Toxicology	Carcogenicity Studies
48,924	0517	1/12/2006		Incoming Agency Correspondence	Meeting Minutes (CINV & PONV Pre-NDA Meeting FDA Responses (Mtg Canceled))
48,924	0517	1/13/2006	"0109"	Response to FDA Request for Information	In Vitro data/results
21-549	0869	1/18/2006		Incoming Agency Correspondence	Acknowledgment Letter of receipt (Labeling Revisions Based on Carco Studies)
21-549	0869	1/25/2006		Other/Periodic Adverse Drug Reaction Report (ADR)	Periodic ADR Report (9/27/05 - 12/26/05)
50,283	0869	1/26/2006	"0391"	Other (specify in description)	Request for Agency Concurrence (RDT Formulation)
21-549	0869	1/30/2006		Amendment to Pending Application	Add approved MEC language (S-008) to the pending PONV sNDA label
21-549	0869	1/31/2006		Other/Pediatric Information	Proposed Pediatric Study Request
48,924	0517	2/1/2006		Incoming Agency Correspondence	Other Agency Correspondence (EMEND IV Tradename Not Recommended)
21-549	0869	2/3/2006		Other/Response to Request for Information	Clarifications on PONV Protocol 090
21-549	0869	2/9/2006		Other/Patent Information	Updated Patent Information (MEC)
21-549	0869	2/10/2006		Incoming Agency Correspondence	Request for Information (Re: Carco Studies)
50,283	0869	2/14/2006	"0392"	Other/Pediatric Information	Revised Proposed Pediatric Study Request & Responses to April 26, 2005 FDA Comments
48,924	0517	2/15/2006	"0110"	General Correspondence	Request for Concurrence Re: DSI files for MK-0517 NDA
22-023	0517	2/22/2006		User Fee Letter	User Fee for Fosaprepitant Dimeglumine NDA 22-023
21-549	0869	2/28/2006		Incoming Agency Correspondence	Request for Information (Table - Protocol Deviations Affecting Analysis Populations)
48,924	0517	2/28/2006	"0111"	Response to FDA Request for Information	Response Re: FDA Trade Name LetterRequest for Type C Teleconference
21-549	0869	3/1/2006		Other/Response to Request for Information	Requests for P090 & P091 CSR Information
21-549	0869	3/9/2006		Other/Response to Request for Information	Protocol 090 & 091 Statistical Datasets
50,283	0869	3/13/2006		Incoming Agency Correspondence	Other Agency Correspondence (FDA accepts RDT biobatch size proposal for formal stability study)

BRIEF DESCRIPTION OF REPRESENTATIVE SIGNIFICANT ACTIVITIES DURING THE REGULATORY PERIOD FOR FOSAPREPITANT

Reg Number	Compound ID	Filing Date	Serial Number	Activity	Description
48,924	0517	3/16/2006	"0112"	Information Amendment - Clinical	Update CIB
48,924	0517	3/23/2006		Incoming Agency Correspondence	Other Agency Correspondence (Trade Name Meeting Confirmation - July 6, 2006)
50,283	0869	3/24/2006		Incoming Agency Correspondence	Other Agency Correspondence (FDA Comments and Recommendations on RDT Protocol 128)
21-549	0869	3/30/2006		Incoming Agency Correspondence	Request for Information (PONV Safety Tables)
22-023	0517	3/31/2006		Original Application	IV Prodrug of Aprepitant - Prevention of CINV
50,283	0869	3/31/2006	"0393"	Protocol Amendment - New Protocol	MEC PM Commitment - Protocol 130
50,283	0869	4/5/2006	"0394"	Information Amendment - Clinical	Revised CIB
21-549	0869	4/13/2006		Other/Response to Request for Information	Request for PONV Safety Tables
50,283	0869	4/19/2006	"0395"	Protocol Amendment - Change in Protocol	Protocol 097-02
50,283	0869	4/21/2006	"0396"	Information Amendment - Chemistry/Microbiology (CMC)	MK-0869 40 mg ODT PBO & update to composition for MK-0869 40 mg Caps
21-549	0869	4/25/2006		Other/Periodic Adverse Drug Reaction Report (ADR)	Periodic Adverse Experience Report 27-Dec-2005 to 3-Mar-2006
48,924	0517	5/1/2006	"0113"	General Correspondence	MRL Regulatory Affairs Change of Address
50,283	0869	5/1/2006	"0397"	General Correspondence	MRL Regulatory Affairs Change of Address
21-549	0869	5/1/2006		Other (specify in description)	MRL Regulatory Affairs Change of Address
21-549	0869	5/2/2006		Incoming Agency Correspondence	Request for Information (List & Status of PM Commitments for EMEND)
22-023	0517	5/4/2006		Other (specify in description)	MRL Regulatory Affairs Change of Address
21-549	0869	5/4/2006		Other/Response to Request for Information	Response to Request for PM Commitment Update
50,283	0869	5/5/2006	"0398"	Response to FDA Request for Information	Comments Re: P128 (ODT BE Study)
21-549	0869	5/23/2006		Annual Report	Capsules Annual Report for 27-Mar-2005 through 26-Mar-2006
50,283	0869	5/24/2006		Incoming Agency Correspondence	Acknowledgment Letter of receipt (Merck Address Change)
22-023	0517	5/31/2006		Incoming Agency Correspondence	Acknowledgment Letter of receipt (Merck Change of Address)
48,924	0517	5/31/2006		Incoming Agency Correspondence	Acknowledgment Letter of receipt (Merck Change of Address)
22-023	0517	6/2/2006		Amendment to Pending Application	Submission of Environmental Assessment
21-549	0869	6/2/2006		Incoming Agency Correspondence	Other Agency Correspondence (Carco Label Update - FDA Draft Labeling Recommendations)
50,283	0869	6/6/2006		Incoming Agency Correspondence	Other Agency Correspondence (MEC P130 Comments and Recommendations)
21-549	0869	6/8/2006		Amendment to Pending Application	Updated Carco Label
21-549	0869	6/8/2006		Amendment to Pending Application	PONV Pediatric Deferral Timeline
50,283	0869	6/8/2006	"0399"	Annual Report	Capsules Annual Report 10-Apr-05 through 9-Apr-06
21-549	0869	6/9/2006		Incoming Agency Correspondence	Approval Letter (Labeling Update Based on Additional Carcogenicity Studies)
21-549	0869	6/15/2006		Incoming Agency Correspondence	Other Agency Correspondence (FDA's Draft Labeling From 6/13/06 Teleconference)
22-023	0517	6/15/2006		Incoming Agency Correspondence	Acknowledgment Letter of receipt
21-549	0869	6/20/2006		Incoming Agency Correspondence	PPI proposed revisions
21-549	0869	6/21/2006		Amendment to Pending Application	Proposed labeling in response to June 15, 2006 FDA fax
21-549	0869	6/23/2006		Amendment to Pending Application	PPI (Proposed Labeling Text, Annotated)
21-549	0869	6/26/2006		Amendment to Pending Application	Revised Label Based on 6/23/06 FDA Recommendation
21-549	0869	6/26/2006		Incoming Agency Correspondence	Other Agency Correspondence: Carton/Container Labeling Comments
	0517	6/26/2006		Original Application	Import Notification for Fosaprepitant Dimeglumine API prior to NDA Approval.
21-549	0869	6/29/2006		Amendment to Pending Application	PONV Ph IV commitment (cytochrome) & submission of carton label, blister pack

BRIEF DESCRIPTION OF REPRESENTATIVE SIGNIFICANT ACTIVITIES DURING THE REGULATORY PERIOD FOR FOSAPREPITANT

Reg Number	Compound ID	Filing Date	Serial Number	Activity	Description
21-549	0869	6/29/2006		Amendment to Pending Application	Structured Product Labeling (SPL)
21-549	0869	6/30/2006		Amendment to Pending Application	Revisions to blister pack based on June 29, 2006 FDA teleconference
21-549	0869	6/30/2006		Incoming Agency Correspondence	Approval Letter (Prevention of Post-Operative Nausea & Vomiting (PONV)); includes Pediatric Commitment and PhIV Commitment for Cytochrome Study
22-023	0517	7/7/2006		Other/Response to Request for Information	EMEND (fosaprepitant dimeglumine) for Injection Tradename Agreements
50,283	0869	7/10/2006	"0400"	Other/IND Reference Authorization	IND Reference Authorization Letter (Dr. L. Einhorn - IND 75,229)
21-549	0869	7/14/2006		Other/Patent Information	Updated Patent Information (PONV)
50,283	0869	7/20/2006	"0401"	Other/IND Reference Authorization	IND Reference Authorization Letter (Dr. A. W. Blackstock - IND 75,333)
21-549	0869	7/24/2006		Other/FPL	FPL for Approved S-010 (PONV) and S-011 (Carco)
21-549	0869	7/26/2006		Incoming Agency Correspondence	Other Agency Correspondence (Acknowledgement of Merck Address Change)
22-023	0517	7/28/2006		Other/Safety Update Report (SUR)	SUR: P016 QTc CSR & Updated Labeling
21-549	0869	8/1/2006		Other/Patent Information	Revised Patent forms 3542 for approved PONV sNDA
22-023	0517	8/3/2006		Incoming Agency Correspondence	Meeting Minutes (Tradename Discussions)
48,924	0517	8/3/2006		Incoming Agency Correspondence	Meeting Minutes (Tradename Discussions)
50,283	0869	8/4/2006		Incoming Agency Correspondence	Comments & Recommendations on MEC Ph IV study
21-549	0869	8/7/2006		Other (specify in description)	Revised Carton & Tri-Fold Labels
22-023	0517	8/17/2006		Incoming Agency Correspondence	Request for Information (CMC)
50,283	0869	8/18/2006	"0403"	Information Amendment - Clinical	SAP for Protocol 097
48,924	0517	8/28/2006	"0114"	Information Amendment - Clinical	Updated CIB
22-023	0517	8/30/2006		Amendment to Pending Application	Draft Pkg Labels (Vial & Carton) updated with Tradename
50,283	0869	8/31/2006	"0404"	Information Amendment - Clinical	Submission of Revised CIB (edition 8)
50,283	0869	9/11/2006	"0405"	Other/Post Marketing Commitment	MEC Phase IV Study - Response to FDA Comments
50,283	0869	9/20/2006	"0406"	Information Amendment - Chemistry/Microbiology (CMC)	CMC update to support Protocol 130
22-023	0517	9/26/2006		Other/Response to Request for Information	Response to 17-Aug-2006 FDA CMC request
22-023	0517	9/29/2006		Amendment to Pending Application	Submission of CMC 18-month stability update to support 24-month shelf-life
21-549	0869	9/29/2006		Labeling Supplement - PAS	Labeling Prior Approval Supplement: Protocol 101 CSR (Post marketing commitment)
21-549	0869	10/13/2006		Other (specify in description)	EMEND CPP for Korea
21-549	0869	10/24/2006		CMC Supplement - CBE 30	CMC update for additional packaging facilities
21-549	0869	10/26/2006		Other/Response to Request for Information	Submission of 40 mg physician sample labeling for DMETS review
22-023	0517	10/27/2006		Other/Background Package	Submission of background package for CMC teleconference
48,924	0517	10/27/2006	"0115"	Other/Meeting Information (other than Background Package)	Request for Type C Meeting
21-549	0869	10/27/2006		Other/Response to Request for Information	Response to FDA request regarding use of 3-drug combination for CINV/HEC
50,283	0869	10/27/2006	"0407"	Protocol Amendment - New Protocol	Submission of Protocol 140 (Post marketing commitment from30-Jun-2006 approval of S-010)
22-023	0517	11/7/2006		Incoming Agency Correspondence	FDA request for information regarding Microbiology section of NDA
50,283	0869	11/8/2006	"0408"	Information Amendment - Chemistry/Microbiology (CMC)	CMC update to support Protocol 130
48,924	0517	11/8/2006		Other/Meeting Information (other than Background Package)	FDA confirmation of Type C meeting re single-dose IV study
50,283	0869	11/13/2006	"0409"	Protocol Amendment - New Protocol	Submission of Protocol 138-00

BRIEF DESCRIPTION OF REPRESENTATIVE SIGNIFICANT ACTIVITIES DURING THE REGULATORY PERIOD FOR FOSAPREPITANT

Reg Number	Compound ID	Filing Date	Serial Number	Activity	Description
22-023	0517	11/20/2006		Other/Meeting Information (other than Background Package)	Submission of meeting summary from 07-Nov-2006 FDA teleconference
48,924	0517	11/22/2006	"0116"	Annual Report	I.V. Annual Report for 29-Sep-2005 through 28-Sep-2006
50,283	0869	11/27/2006	"0411"	Information Amendment - Chemistry/Microbiology (CMC)	Submission of CMC section for EMEND 40 mg placebo to support Protocol 138
22-023	0517	12/5/2006		Incoming Agency Correspondence	FDA Request for Information re. biopharmacology section of NDA
22-023	0517	12/7/2006		Amendment to Pending Application	CMC update of specifications and lyophilization parameters per 07-Nov-2006 FDA teleconference
21-549	0869	12/7/2006		Incoming Agency Correspondence	Acknowledgment Letter of receipt for S-013
22-023	0517	12/8/2006		Amendment to Pending Application	Response to FDA CMC questions from 17-Oct-2006 and 07-Nov-2006.
50,283	0869	12/8/2006		Incoming Agency Correspondence	FDA statistical review comments regarding protocol 130 (phase IV study)
50,283	0869	12/8/2006		Incoming Agency Correspondence	FDA comments to 11-Sep-2006 response re. Phase IV study (Protocol 130)
48,924	0517	12/18/2006	"0117"	Other/Background Package	Background package for Agency review, in accordance with FDA's Guidance for Industry: "Formal Meetings with Sponsors and Applicants for PDUFA Products"
22-023	0517	12/19/2006		Other/Response to Request for Information	Submission of response to 05-Dec-2006 FDA biopharm request for information
48,924	0517	1/9/2007		Incoming Agency Correspondence	Preliminary FDA comments for 11-Jan-2007 face-to-face meeting
21-549	0869	1/16/2007		Incoming Agency Correspondence	FDA (DMETS) response to MRL request for labeling feedback
50,283	0869	1/19/2007	"0412"	Other/Post Marketing Commitment	Response to 08DEC2006 quest on Ph IV study (prot 130); response emailed 18jan07
22-023	0517	1/24/2007		Incoming Agency Correspondence	Request for Information from FDA microbiology reviewer
21-549	0869	1/25/2007		Incoming Agency Correspondence	FDA Request for Information regarding BE studies performed by MDS Pharma.
22-023	0517	1/26/2007		Incoming Agency Correspondence	FDA confirmation of 3-month PDUFA date extension for NDA review
21-549	0869	1/30/2007		Incoming Agency Correspondence	Acknowledgment Letter of Receipt for S-012 (Vinorelbine label supplement)
22-023	0517	2/2/2007		Incoming Agency Correspondence	FDA Request for Information regarding clinical pharmacology section of NDA
48,924	0517	2/7/2007		Incoming Agency Correspondence	FDA meeting minutes from 11-Jan-2007 Type C meeting
48,924	0517	2/9/2007	"0118"	Other/Meeting Information (other than Background Package)	Type C meeting request to discuss single-dose IV study
22-023	0517	2/12/2007		Other/Response to Request for Information	Response to FDA request for information regarding dexamethasone dose
48,924	0517	2/15/2007		Incoming Agency Correspondence	FDA response to MRL 09-Feb-2007 Type C meeting Request
22-023	0517	2/21/2007		Amendment to Pending Application	CMC update to original NDA
21-549	0869	2/21/2007		Other/Response to Request for Information	Response to FDA request for information regarding MDS Pharma
	0517	2/23/2007		Import - Original Application	EMEND (Blended Beads)
50,283	0869	2/23/2007		Incoming Agency Correspondence	FDA comments/recommendations to 19-Jan-2007 MRL response to FDA info request - statistics
48,924	0517	3/2/2007	"0119"	Other/Meeting Information (other than Background Package)	January 11, 2007 MRL Meeting Minutes
48,924	0517	3/16/2007	"0120"	Other/Background Package	Type C Meeting Background Package
22-023	0517	3/16/2007		Other/Response to Request for Information	Response to FDA information requests - AE listings/Microbiology

BRIEF DESCRIPTION OF REPRESENTATIVE SIGNIFICANT ACTIVITIES DURING THE REGULATORY PERIOD FOR FOSAPREPITANT

Reg Number	Compound ID	Filing Date	Serial Number	Activity	Description
22-023	0517	3/21/2007		Amendment to Pending Application	Submission of updated 1-month stability data for Batch 4 (lot A25808)
21-549	0869	4/2/2007		Incoming Agency Correspondence	Approvable Letter for Vinorelbine labeling sNDA
21-549	0869	4/2/2007		Incoming Agency Correspondence	Approvable Letter - for label change based on PMC #2
48,924	0517	4/18/2007		Incoming Agency Correspondence	Other Agency Correspondence-Preliminary response to MRL Bk Pk questions for April 19 meeting
21-549	0869	4/20/2007		Other/Response to Request for Information	S-012/Analytical methods and validation reports requested in April 2, 2007 FDA letter
21-549	0869	4/25/2007		Incoming Agency Correspondence	Approval Letter for CBE-30 (additional packaging sites)
22-023	0517	5/3/2007		Incoming Agency Correspondence	Approvable Letter- Requesting 3 month stability data
21-549	0869	5/10/2007		Incoming Agency Correspondence	S-012/Request for Information Re: Incomplete response to approvable letter (Vinorelbine)
48,924	0517	5/10/2007		Incoming Agency Correspondence	FDA letter containing minutes to a face to face meeting held with Merck on April 19, 2007
22-023	0517	5/11/2007		Other/Intent to Amend	Intent to Amend in response to Approvable letter for NDA 22-023
21-549	0869	5/16/2007		Other/Response to Request for Information	S-012 - Complete response to April 2 Approvable, and May 10, 2007 FDA request letter
48,924	0517	5/18/2007	"0121"	Other/Meeting Information (other than Background Package)	MRL Minutes of April 19, 2007 meeting
48,924	0517	5/23/2007		Incoming Agency Correspondence	FDA Comments Re: Proposed Clinical Study.
21-549	0869	5/25/2007		Other/Periodic Adverse Drug Reaction Report (ADR)	27-MAR-2006 through 26-MAR-2007
21-549	0869	5/31/2007		Annual Report	Capsules Annual Report for 27-Mar-06 to 26-Mar-07
50,283	0869	6/5/2007	"0413"	Annual Report	Capsules Annual Report for 10-Apr-06 through 9-Apr-07
21-549	0869	6/5/2007		Incoming Agency Correspondence	FDA letter acknowledging receipt of Merck Reponse Re: 40, 80 and 125
48,924	0517	6/14/2007	"0122"	Protocol Amendment - New Protocol	Protocol 018
48,924	0517	6/18/2007	"0123"	Information Amendment - Chemistry/Microbiology (CMC)	Drug Substance and Product 115 mg vial
48,924	0517	6/18/2007	"0124"	Other/IND Reference Authorization	IND Cross Reference Letter David Boorsook, MD, Ph.D for IND 77, 786
50,283	0869	7/16/2007	"0415"	Protocol Amendment - Change in Protocol	Protocol Amendment 130-01
22-023	0517	7/27/2007		Other/Response to Request for Information	Response to FDA Approvable Letter of May 3, 2007
50,283	0869	8/9/2007	"0416"	Other (specify in description)	IND Reference Authorization - Barbara Murphy, MD
50,283	0869	8/20/2007	"0417"	General Correspondence	RE:PMC and Pediatric Study - Request for Extension
21-549	0869	8/20/2007		Other/Post Marketing Commitment	RE:PMC for Pediiatric Study - Request for Extension to Dec 2009
50,283	0869	8/29/2007	"0418"	Information Amendment - Clinical	Additional Sites for 130-007
22-023	0517	9/28/2007		Other/Response to Request for Information	Response to FDA Approvable Letter - 3 Month Stability Data
50,283	0869	10/1/2007	"0419"	Information Amendment - Clinical	Addition of Site - Protocol 130-0007
48,924	0517	10/12/2007	"0126"	Other/Special Protocol Assessment	Request for Special Protocol Assessment Protocol 017
22-023	0517	10/18/2007		Incoming Agency Correspondence	FDA Request Letter Re: July 27, 2007 MRL Response
22-023	0517	11/1/2007		Other/Response to Request for Information	Response to Oct.18, 2007 Request Re: Micro data
21-549	0869	11/6/2007		Incoming Agency Correspondence	S012- FDA recommendations to proposed labeling.
21-549	0869	11/9/2007		Other/Response to Request for Information	S-012 Response to FDA fax of Nov 6, 2007 Re: Proposed labeling
21-549	0869	11/15/2007		Incoming Agency Correspondence	S-012 -Approval for vinorelbine interaction supplement/PMC #2

BRIEF DESCRIPTION OF REPRESENTATIVE SIGNIFICANT ACTIVITIES DURING THE REGULATORY PERIOD FOR FOSAPREPITANT

Reg Number	Compound ID	Filing Date	Serial Number	Activity	Description
21-549	0869	11/15/2007		Incoming Agency Correspondence	S-012 - FDA approval letter for concommitant use of vinorelbine
22-023	0517	11/16/2007		Other/Meeting Information (other than Background Package)	Summary of Nov. 9, 2007 FDA Teleconference
48,924	0517	11/21/2007	"0128"	Annual Report	Annual Report for 29-Sep-2006 to 28-Sep-2007
48,924	0517	11/29/2007		Incoming Agency Correspondence	FDA letter providing SPA comments for Protocol 017
22-023	0517	12/4/2007		Other/Response to Request for Information	Data from Microbial Assessment Study, per FDA Request
21-549	0869	12/7/2007		Other/FPL	S-012 - SPL and FPL for Vinorelbine supplement
21-549	0869	12/11/2007		Incoming Agency Correspondence	FDA letter acknowledging receipt of submissions for postmarketing study commitment
50,283	0869	12/11/2007	"0423"	Other/Post Marketing Commitment	Postmarketing Commitment to submit P140
22-023	0517	12/17/2007		Amendment to Pending Application	Revision to Draft Packaging Components (vial label, 1x-, and 10x cartons)
21-549	0869	12/17/2007		Other/Post Marketing Commitment	CSR for Protocol 140 in fulfillment of PMC for PONV
21-549	0869	12/27/2007		Incoming Agency Correspondence	FDA letter regarding Post Marketing Commitments for the NDA.
48,924	0517	1/4/2008	"0129"	Information Amendment - Clinical	Updated CIB- Edition 4
22-023	0517	1/7/2008		Incoming Agency Correspondence	FDA letter acknowledging receipt of July 27, 2007 resubmission to NDA 22-023
48,924	0517	1/9/2008	"0130"	Protocol Amendment - New Protocol	PN 017-00
22-023	0517	1/17/2008		Other/Pediatric Information	Proposed Pediatric Study Request
50,283	0869	1/18/2008	"0424"	Information Amendment - Chemistry/Microbiology (CMC)	CMC Update to the composition of the placebo for Dexamethasone Tablets
22-023	0517	1/18/2008		Other/Pediatric Information	Proposed Pediatric Study Request
48,924	0517	1/22/2008	"0132"	Information Amendment - Chemistry/Microbiology (CMC)	CMC amendment in support of MK-0517 for Injection, PN017
22-023	0517	1/24/2008		Other/Pediatric Information	Proposed Pediatric Plan
22-023	0517	1/24/2008		Other/Post Marketing Commitment	Post Marketing Commitment
22-023	0517	1/25/2008		Amendment to Pending Application	Revision to proposed USPC, USPPI,& trade packaging components (1X-,10X- cartons and vial label)
22-023	0517	1/25/2008		Incoming Agency Correspondence	FDA approval letter for NDA 22-023 Emend (fosaprepitant dimeglumine) for Injection, 115mg
22-023	0517	1/25/2008		Other/Post Marketing Commitment	Post marketing commitment including date that SAP will be provided